SYNTHETIC STUDIES ON PROSTAGLANDINS

"SYNTHESIS OF A NEW THIA-PGE1 ANALOG"

BY

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ABSTRACT

A PGE_1 analog, namely (±)-trans-2-(6'-carbomethoxyhexyl)-3-(E-3"-thia-1"-octene)-4-hydroxycyclopentanone **71**, has been prepared for the first time. Towards the synthesis of this compound, several synthetic approaches aimed at the preparation of the required acetylenic and E-halovinylic sulfides as building blocks were investigated.

Among all the methods examined, it appeared evident that the best route to ethynyl n.pentyl sulfide **81** is *via* a double dehydrohalogenation of the corresponding 1,2-dibromoethyl sulfide with sodium amide in liquid ammonia. In addition, the isomerically pure E-2-iodoethenyl n.pentyl sulfide **85** is conveniently prepared in high yield and stereoselectivity by hydrozirconation-iodination of the terminal ethynyl sulfide **81**. The classical hydroalumination and hydroboration reactions for the preparation of vinyl halides from alkynes gave only small yields when applied as methods towards the synthesis of **85**.

The building block 2-(6'-carbomethoxyhexyl)-4-hydroxy-2-cyclopentenone (±)-**1** carrying the upper side-chain of prostaglandin E_1 was prepared by a step-wise synthesis involving transformations of compounds possessing the required carbocyclic framework (see scheme 27). The synthesis proved to be convenient and gave a good overall yield of (±)-**1** which was protected as the THP-derivative **37** or the siloxy derivative **38**.

With the required building blocks **81** and **37** in hand, the target 15-thia-PGE_1 analog (±)-**71** was prepared *via* the in *situ* higher

cuprate formation-conjugate addition reaction. This method proved to be convenient and stereospecific. The standard cuprate method, involving an organocuprate reagent generated from an isolated vinyl iodide, did not work well in our case and gave a complicated mixture of products.

The target compound will be submitted for assessment of biological activity.

ACKNOWLEDGEMENTS

I would like to express my sincere appreciations to Dr. H. L. Holland for his enthusiasm, encouragement and supervision throughout the course of this work.

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To My Parents

For Their

Love And Never-ending Support

Throughout The Years

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INTRODUCTION

I - GENERAL:

Prostaglandins are biologically active lipid acids with a C_{20} skeleton derived from poly-saturated acids.[1] These physiologically important compounds are involved in vital defense processes such as inflammation, tissue repair, and the immune response.

I-1. History of prostaglandins.

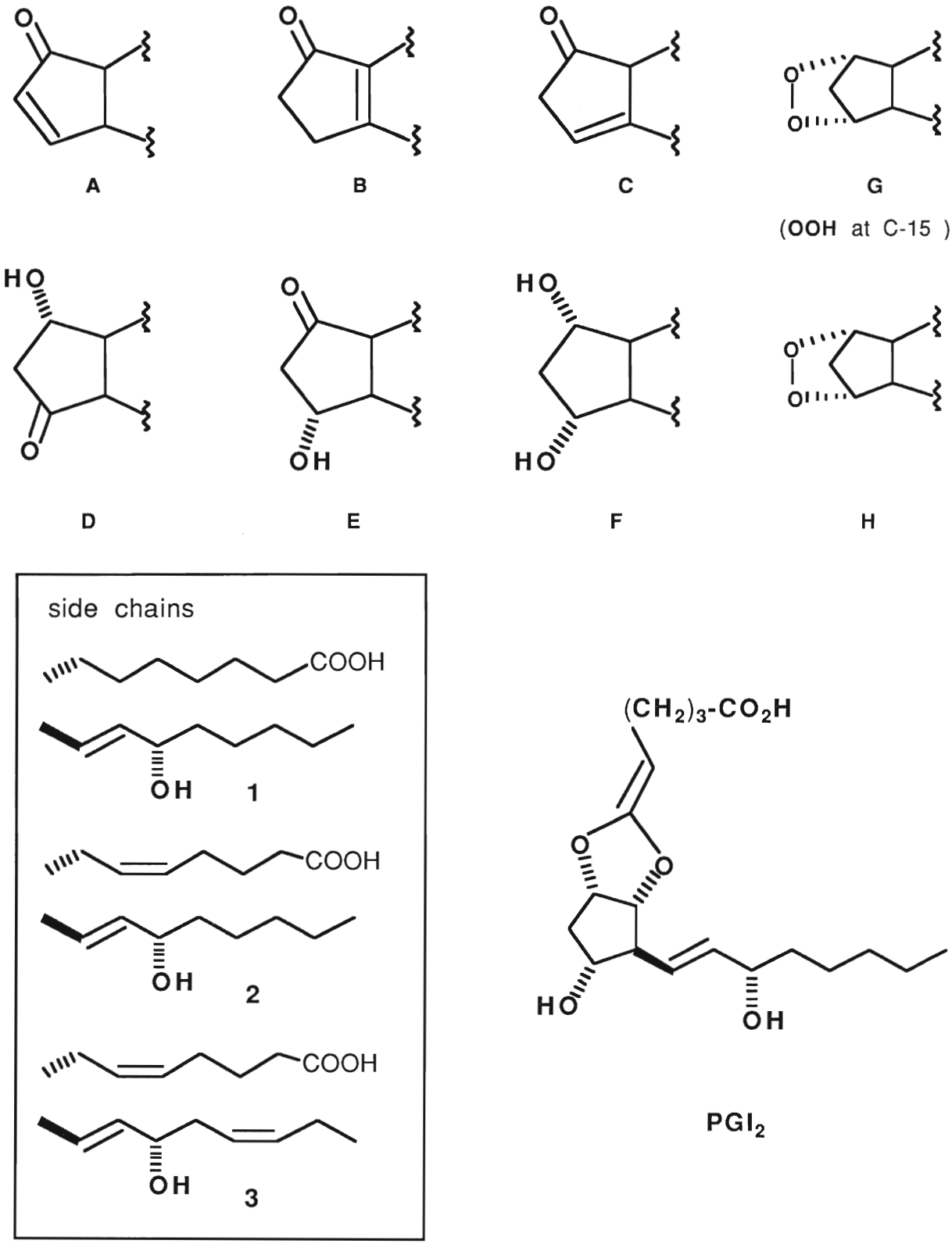
The scientific history of prostaglandins goes back to 1930 when Raphael Kurzrok and Charles Lieh reported that lipid fractions isolated from human semen induced contraction and relaxation of the human uterus.[2] It was in 1935 that the Swedish scientist von Euler suggested the name prostaglandin for the active component because he found trace amounts of it in prostate gland tissue.[2]

Because of the small quantities of the active materials that were available and the lack of advanced chromatographic and spectroscopic techniques, it was not until 1962 that the first structural and stereochemical elucidations of PGs were done.[2]

I-2. Nomenclature of PGs.

There is a system of nomenclature to describe the different types of prostaglandins. They are divided into nine classes designated by letters **A** to I depending on the functionalization of the cyclopentane ring (scheme 1). The numerical subscripts refer to the number of unsaturated bonds in the side chains. The three series of prostaglandin E (PGE) are shown in scheme 2. The numbering of prostaglandins starts by giving the number 1 to the carbon atom of the principle group as shown for PGE_1 in scheme 2.

functionalization of the cyclopentane ring in natural PGs



Scheme 1 : Classification of the prostaglandins (PGs). PGI_2 is prostacyclin

Finally, the subscripts α and β refer to the configuration of the substituents in the ring. Note the similarities among all PGs types . All natural PGs have a double bond with trans configuration at the 13,14 position and a hydroxyl group with α-configuration at C-15.

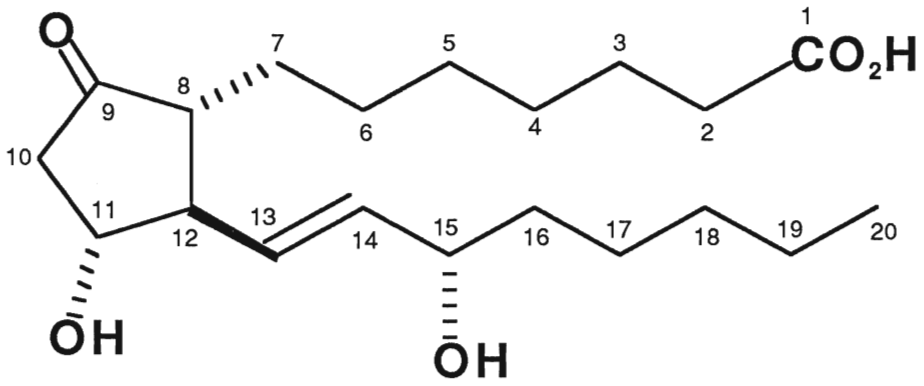
I-3. **Objective of the review.**

In spite of the extensive research done on the synthesis of all types of prostaglandins and their different analogues, this short review will concentrate only on the synthesis of the E-series prostaglandins and some of their analogues. Specifically, this report will present an up to date review of the synthetic methods involving the conjugate addition approach that is used to synthesize the E-series prostaglandins and their analogues with modified side chains only. Although the report will adopt a format that will concentrate mainly on the chemistry of the above mentioned series of compounds, it will also consider the biological activities of these compounds where appropriate.

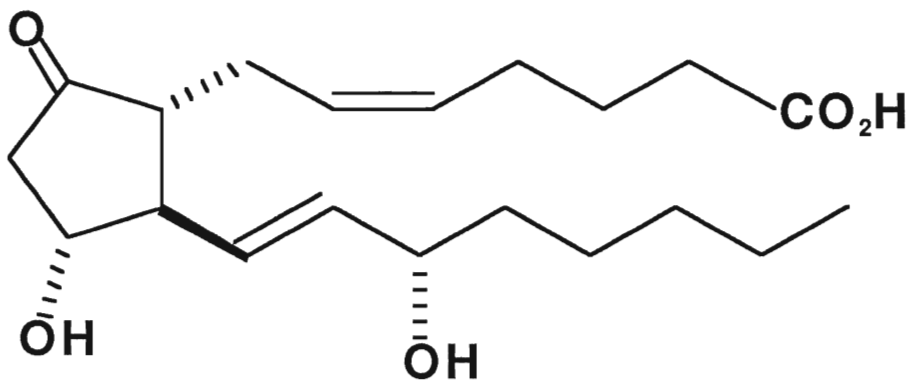
The E-series prostaglandins was chosen as the subject of this review mainly for two reasons:

1) The E-series PGs are the most widely studied.
2) Off all the PGs, the E-series have probably the widest spectrum of activity.

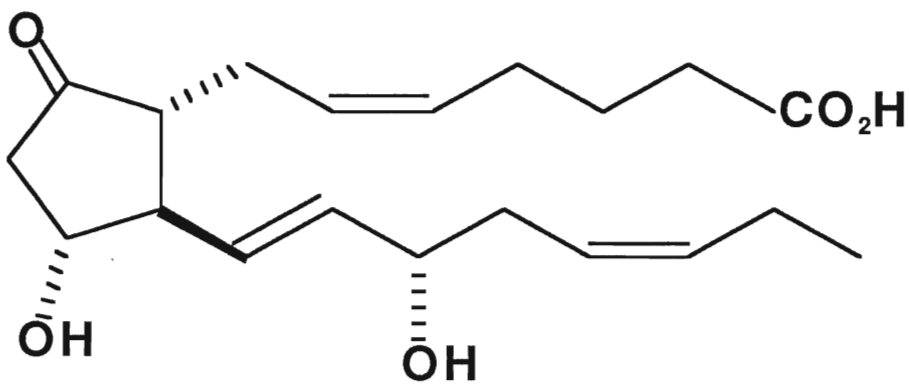
Furthermore, the synthesis of the E-series prostaglandins *via* the conjugate addition approach is presented here because it is probably the most efficient route to prostaglandins. For convenience and flexibility, this approach is also far more advantageous than the other common synthetic routes involving the use of polycyclic



PGE1



PGE2



PGE3

Scheme 2 : the three natural series of prostaglandin E (PGE)

intermediates. The advantages will become clear when the syntheses are presented.

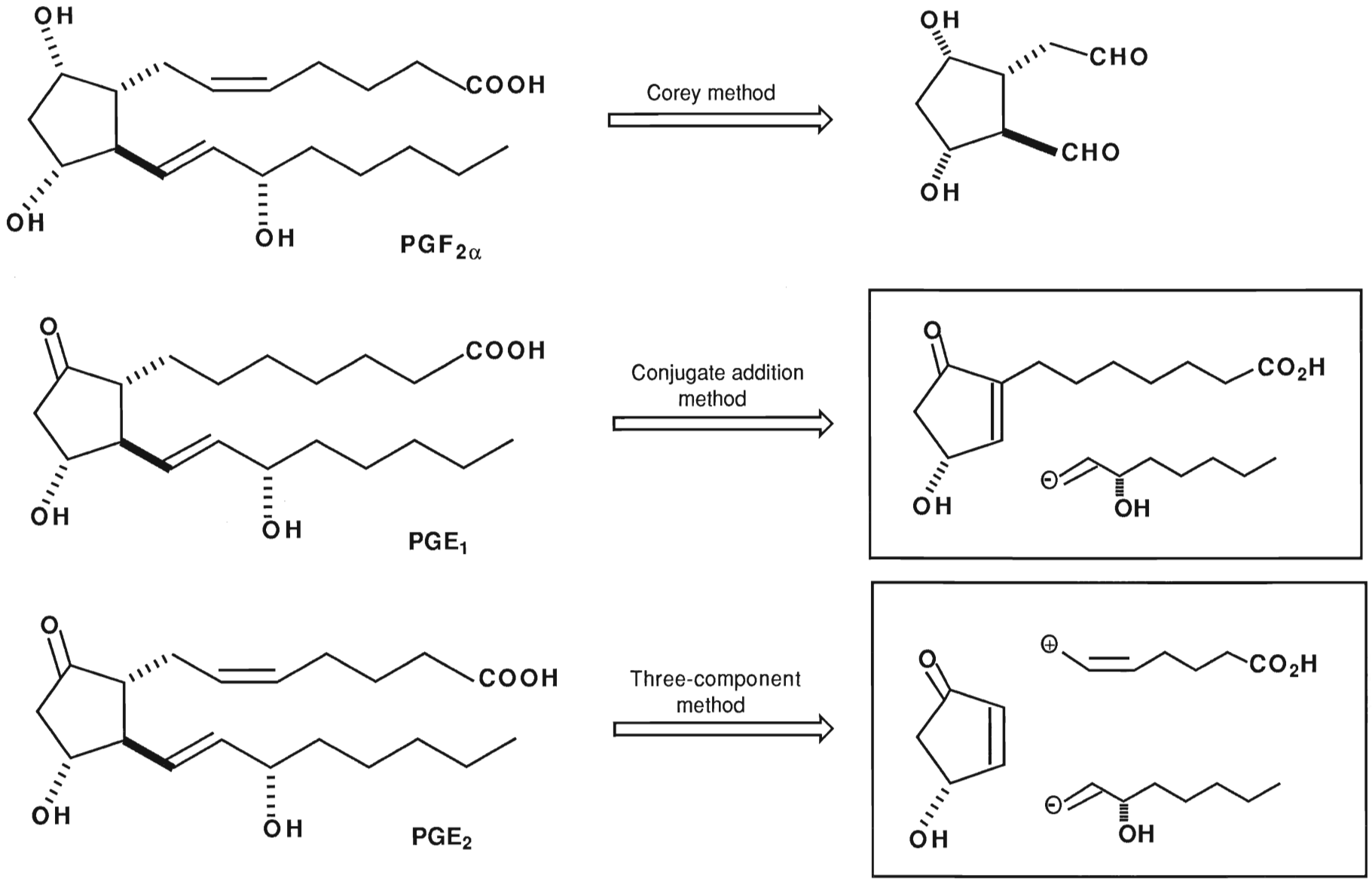
II - THE SYNTHESIS OF NATURAL E-SERIES PROSTAGLANDINS.

Because of the increasing demand for prostaglandins, biosynthesis which used to be the only source of these compounds became inadequate to meet this demand. Therefore, the development of an efficient PG chemical synthesis has been necessary as the only way to provide sufficient quantities of these compounds.

A simplified retrosynthetic analysis of $PGF_{2\alpha}$, PGE_1, and PGE_2 reveals the synthons shown in scheme 3. The Corey synthesis[3] which consists of a two-fold Wittig type chain extension of the chiral dialdehyde synthon shown in scheme 3 will not be discussed here since it is developed through the use of cyclic systems. The two other methods suggested by the retrosynthetic analysis both involve the development of the synthesis *via* conjugate addition type reactions and hence they are the subject of this review.

II-1. The two component conjugate addition method :

This approach is an attractive route to the synthesis of prostaglandins. The method involves a conjugate addition of the lower side chain to the cyclopentenone derivative in which the upper side chain is already installed, scheme 3 . This approach was initially developed by Sih[4] and Fried[5] and has been used successfully for the synthesis of PGE_1. In order to perform such a synthesis building blocks have to be obtained first.



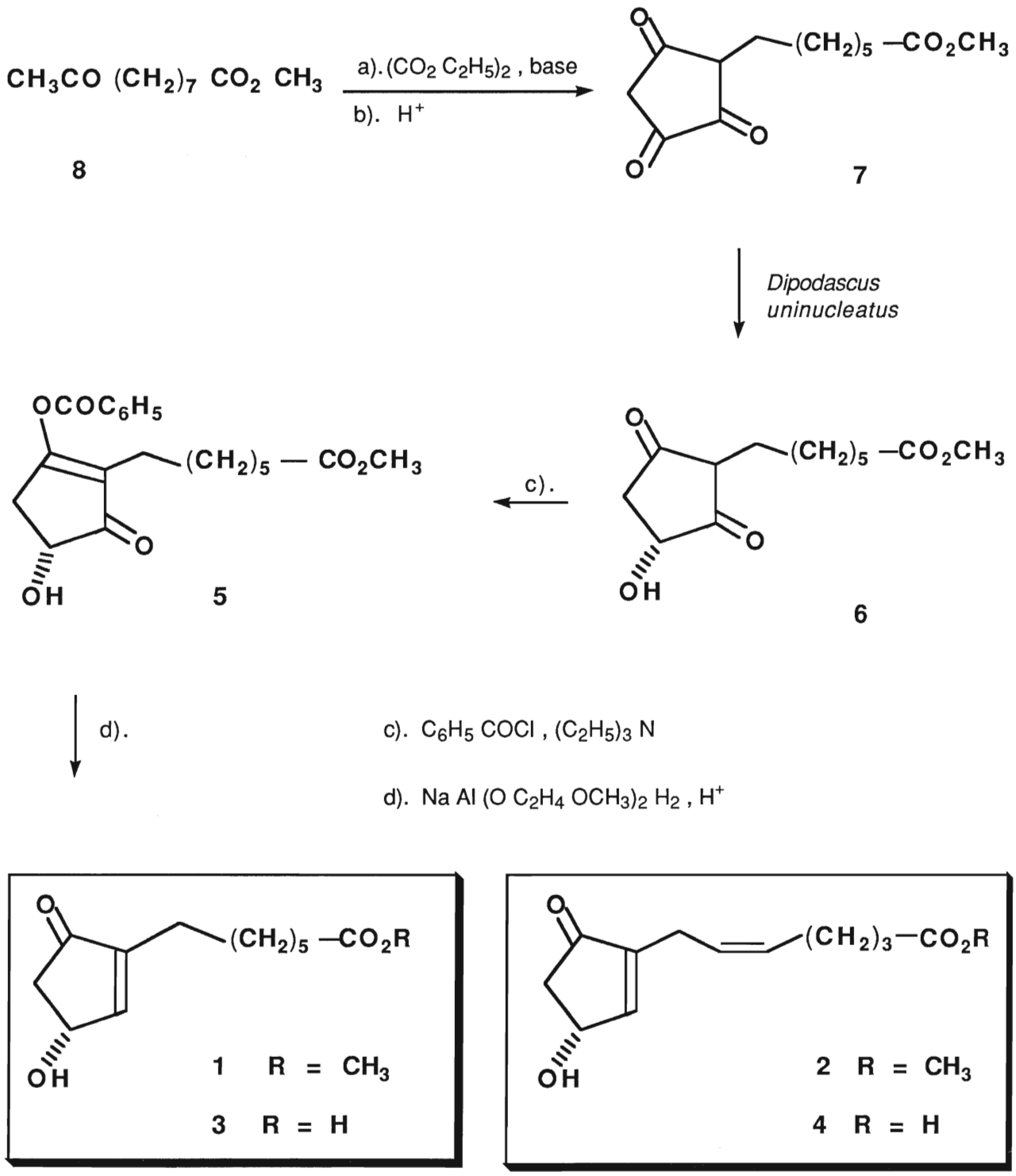
Scheme 3 : Possible retrosynthetic routes to PGs

II -1.1. **Access to chiral building blocks.**

The prostanoid intermediate **3** has been the subject of extensive synthetic work for the past two decades. There is now a large number of syntheses for preparing this compound (or its ester derivatives) necessary for the conjugate addition leading to natural PGE_1. This review, however, will only concentrate on novel synthetic routes although some of the others will be cited.

There are now several synthetic approaches for obtaining the optically active synthons **1** and **2** necessary for the conjugate addition leading to natural PGE_1 and PGE_2, respectively. The first route to be considered for the synthesis of the chiral synthon **1** was developed by Sih and co-workers.[4] They used the triketone **7** as the key synthon for the preparation of the required cyclopentenone. The triketone is easily prepared from the decanoic acid derivative **8** by reaction with dimethyl oxalate in the presence of potassium t-butoxide (see scheme 4).

Enzymatic reduction of **7** using *Dipodascus uninucleatus* afforded the alcohol **6** with the required **R**-configuration. One would also expect that chemical monoreduction of the C=O bond at C-11 (prostaglandin numbering) in **7** should proceed with high degree of regioselectivity since it is the least sterically hindered. Sih then treated the **R**-alcohol **6** with a mild base and an acylating agent such as benzoyl chloride and achieved a selective benzoylation obtaining **5.** The synthesis was then finished by the reduction of **5** with sodium bis (2-methoxyethoxy) aluminium hydride followed by allylic rearrangement in acid to give the required synthon **1**.

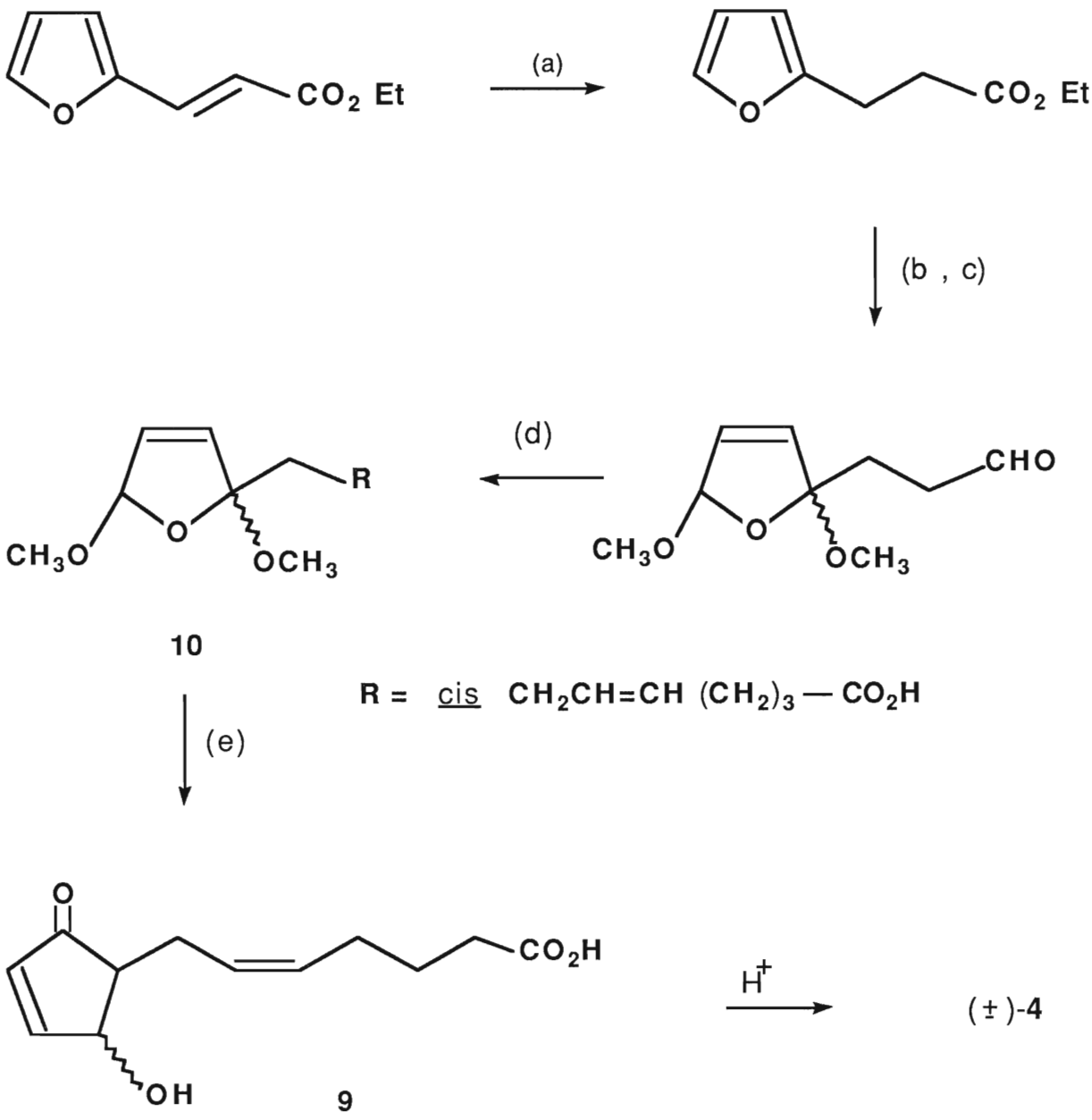


Scheme 4. synthesis of the optically active 2-substituted (**R**)-4-hydroxy 2-cyclopentenone **1** *via* asymmetric microbial reactions.

Using this approach the chiral cyclopentenone synthon **2** necessary for the conversion into PGE_2 was prepared in a similar sequence of reactions from the corresponding triketone. Other synthetic routes for the 2-substituted-4-hydroxy cyclopentenones exist. Stork and Takahashi[6] used D-glyceraldelyde as a chiral source for the 4-(**R**)-configuration in **1**. Gill and Rickards[7] prepared the chiral 4-hydroxycyclopent-2-enone **1** starting from phenol·

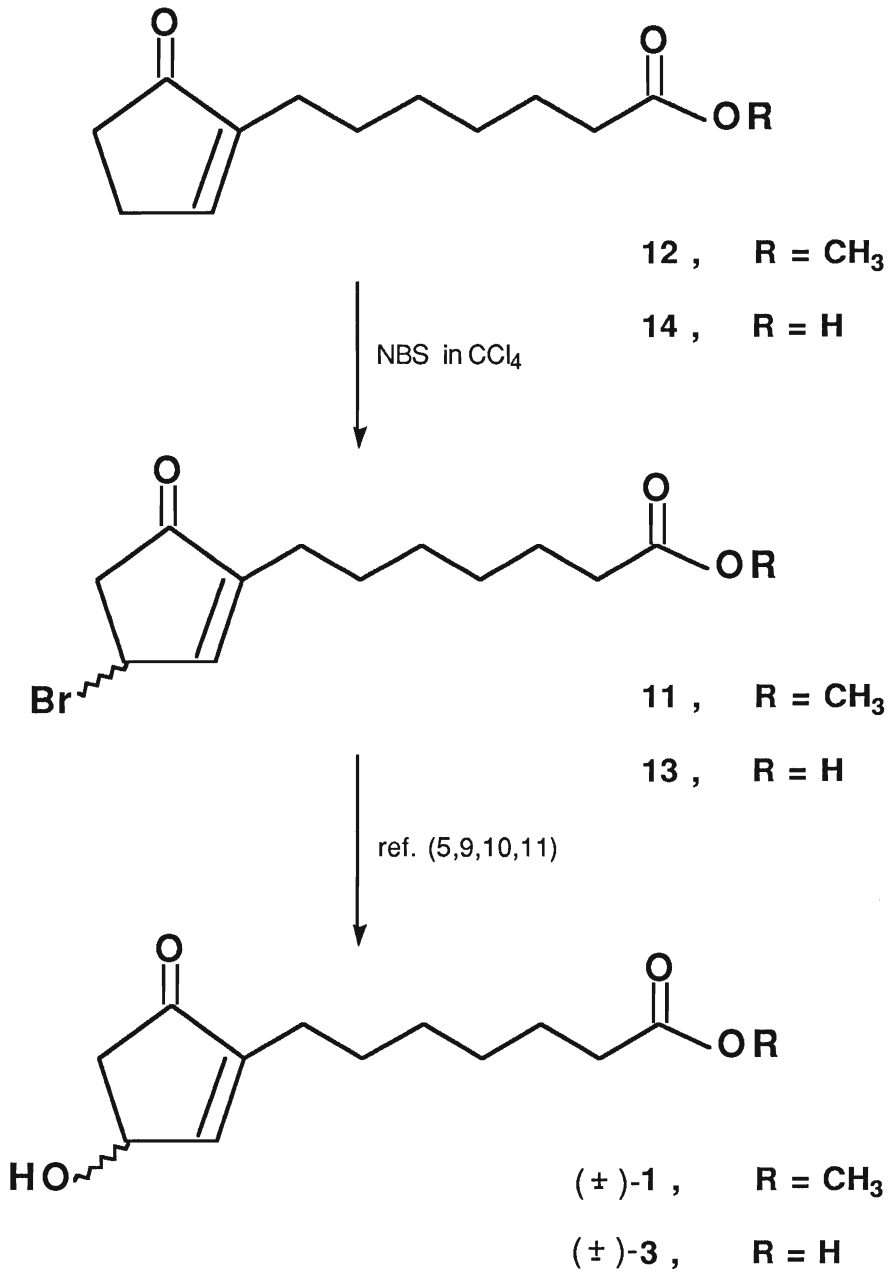
A novel approach to the synthesis of (±)- **4,** the acid derivative of (±))-**2**, was developed by Floyd [8] and is illustrated in scheme 5. The key intermediate in the synthesis of (±)-**4** is the 2,5-dihydro-2,5-dimethoxyfuran (±)-**10** which is synthesized by standard methods as shown. Thus (±)-**10** was subjected to an acid-catalyzed rearrangement using phosphate buffer (pH 6) in aqueous dioxane at 92° C to give presumably an aldehyde intermediate which underwent an aldol cyclization to give (±)-**9**. Isomerization of (±)-**9** then gave (±)-**4** which could be esterified in the usual way to give (±)-**2** .

A more general and convenient approach to the synthesis of racemic **1** is based on the preparation of the 2-alkylated cyclopentenone **12** followed by hydroxylation at C-4 of the 4-bromo-2-cyclopenten-1-one intermediate **11** prepared by the allylic bromination[9] of **12**. The allylic hydroxylation of the 2-substituted 4-bromo-2-cyclopentene-1-one **11** has been achieved in several ways. These hydrolysis methods include the use of silver perchlorate in aqueous acetone[5], aqueous silver fluoroborate[9], siver oxide in aqueous acetone[10], and recently water in refluxing dioxane[11] (scheme 6).



Reagents : (a) H_2, Ni ; (b) Br_2 , MeOH ; (c) Bu^i_2AlH, -70° C ;
(d) $Ph_3PCH\ (CH_2)_3CO_2^-$; (e) H^+ then base

Scheme 5 : Synthesis of racemic **4** (Floyd's synthesis) needed for the construction of PGE_2.

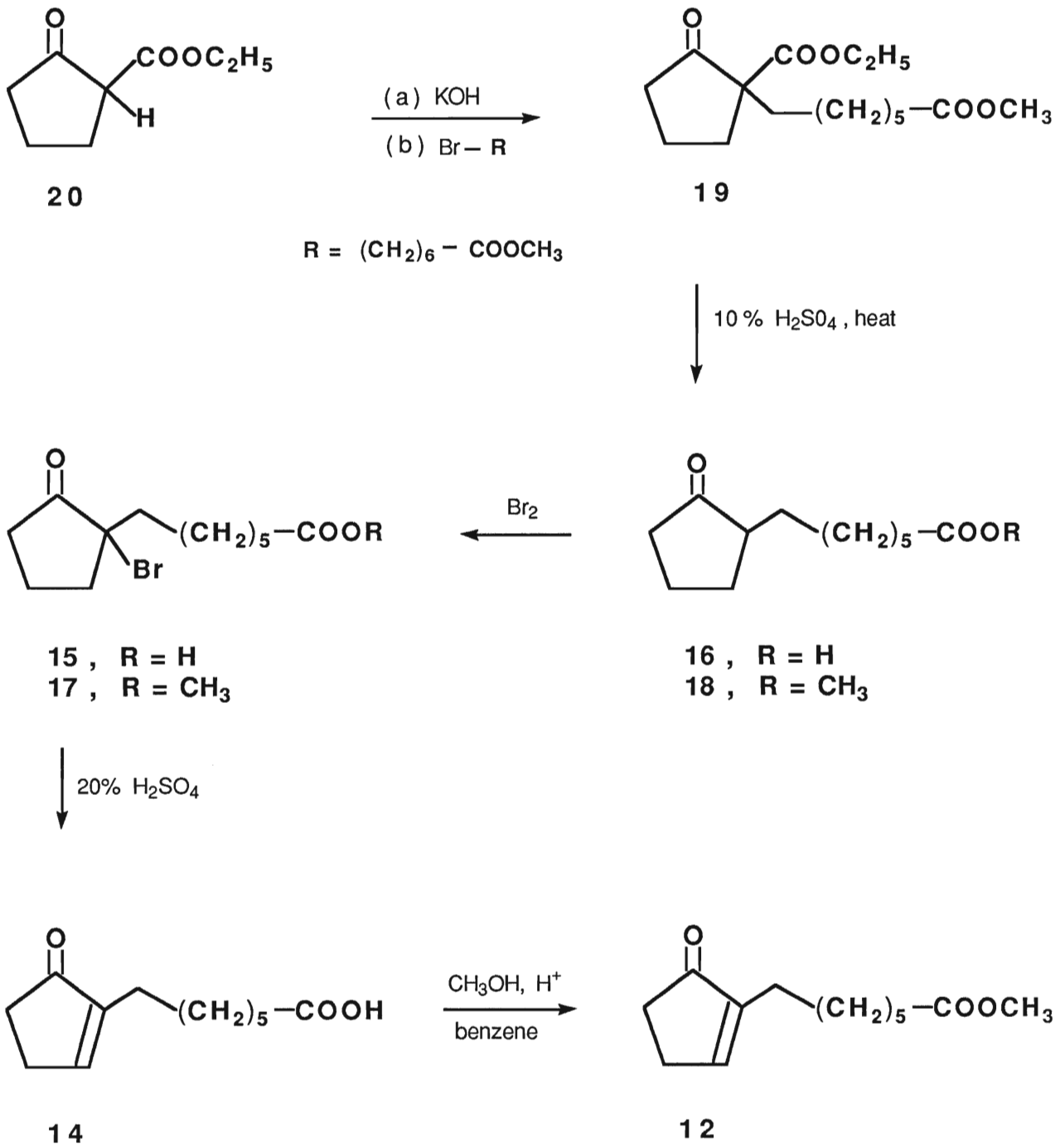


Scheme 6 : Preparation of racemic 4-hydroxy cyclopentenones **1** and **3** from the corresponding enones.

Direct stereospecific hydroxylation of **14** to give the optically active hydroxy acid **3** has been achieved enzymatically with *Aspergillus niger.*[12] There are now a number of methods for resolving racemate **1** and **2**. In 1973, a successful method was reported[13] for resolving (±)-**1** after oxime formation with (**R**)-2-aminooxy-4-methylvaleric acid and then chromatographic separation of the diastereomeric mixture followed by hydrolysis to give the chiral synthon **1**.

The synthesis of the 2-substituted cyclopentenone **12** as a useful prostanoid synthon and a precursor of **1** has also been the object of intensive investigations. These synthetic methods may best be described as those methods based on the transformation of compounds already possessing the carbocyclic framework, or those based on the preparation of certain γ–dicarbonyl compounds which successively undergo catalysed cyclizations.

According to the first approach, Bagli and co-worker[14] prepared **12** in a sequence of reactions as illustrated by scheme 7. Thus, ethyl 2-oxocyclopentane carboxylate **20** was alkylated with methyl 7-bromo-heptanoate to give the keto diester **19** which was hydrolyzed and decarboxylated to the keto acid **16**. The corresponding enone **14** was formed by bromination of **16** to give the bromo derivative **15** which was subjected to elimination under acidic conditions to afford the enone acid **14** . Esterification in the usual way then provided **12**.

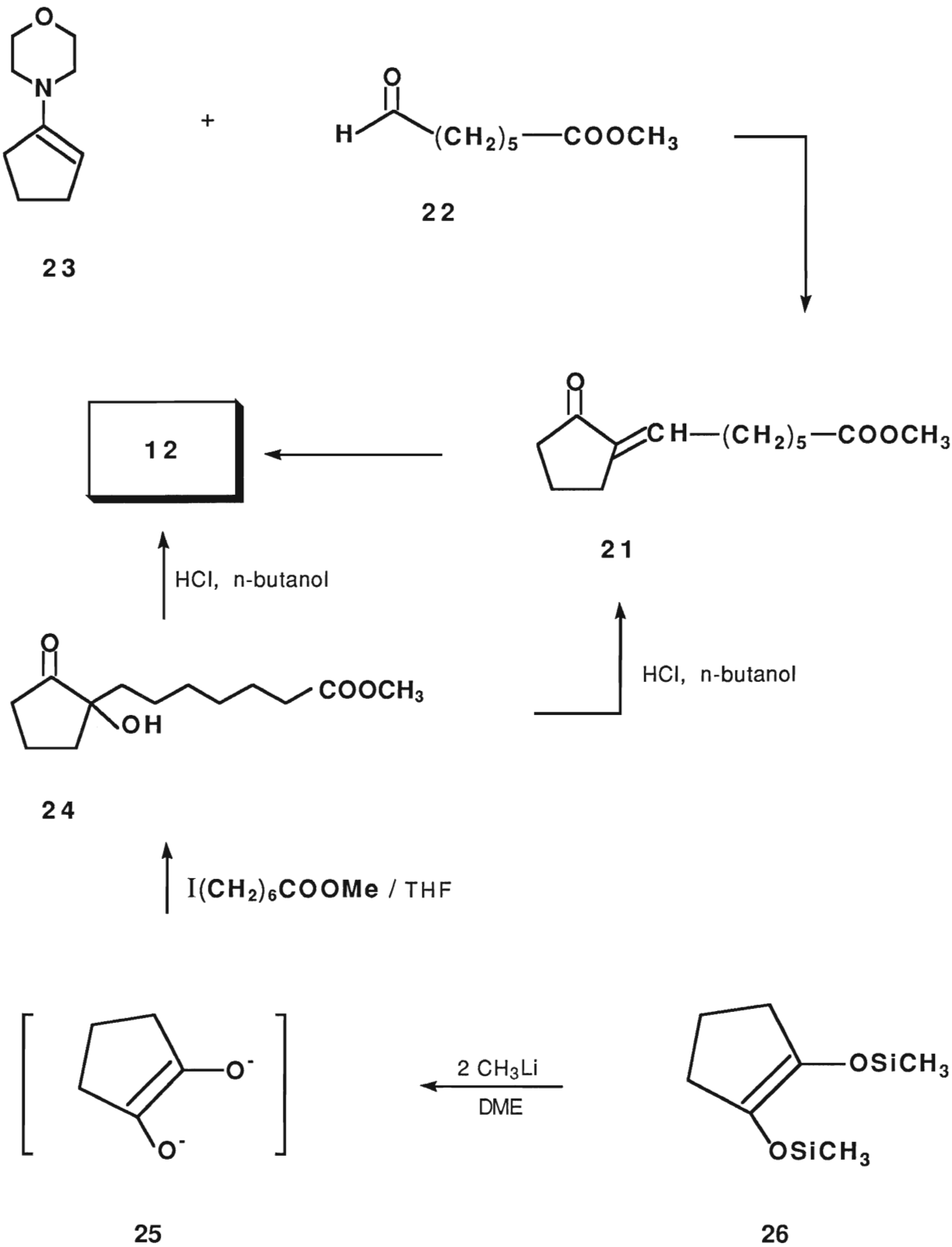


Scheme 7 : Bagli's route to 2-substituted cyclopentenones, **14** and **12**.

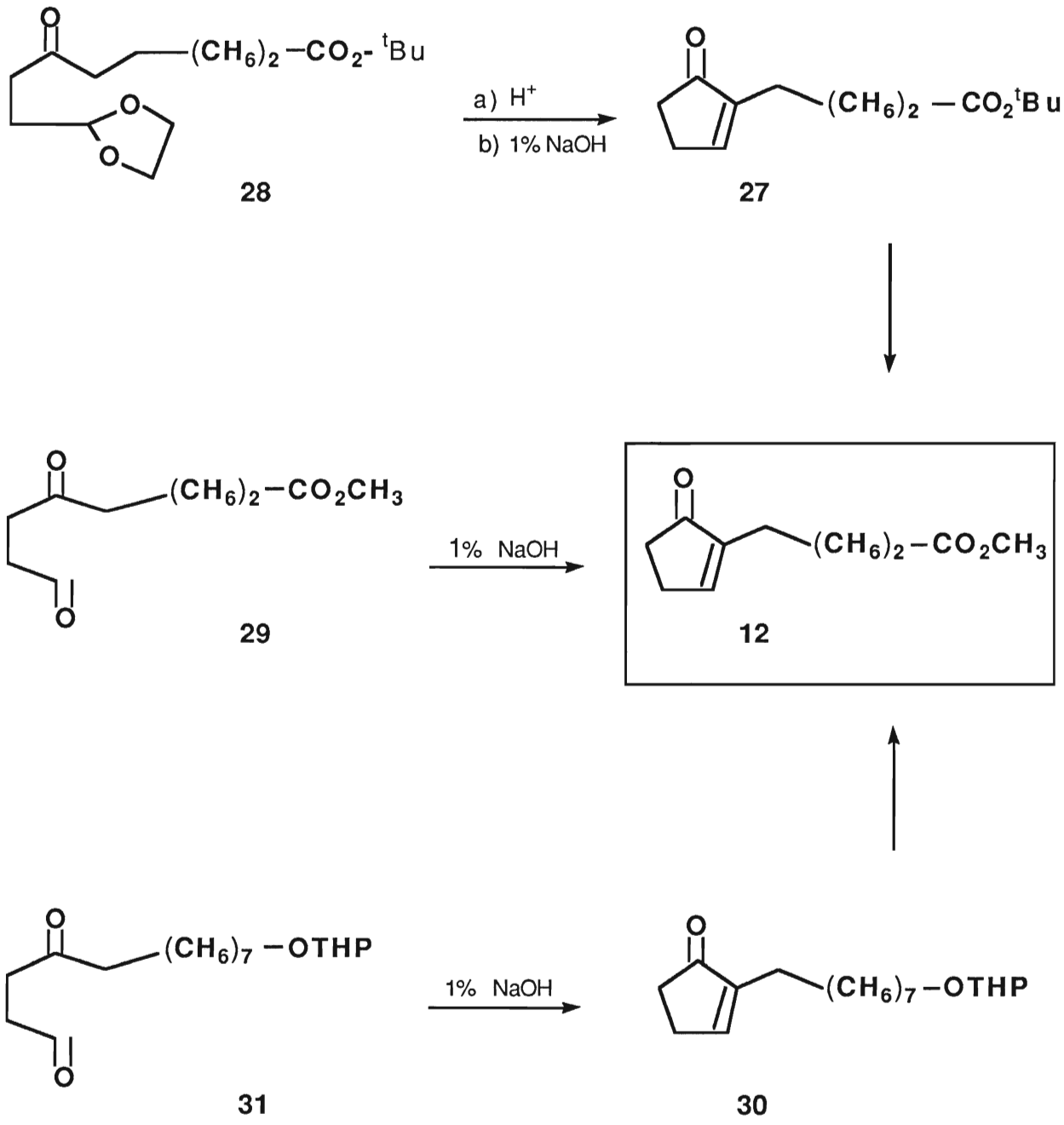
Because this synthetic sequence was a straightforward route to **12** and subsequently to the prostanoid intermediate **1**, it was improved by several researchers. For example, the alkylation step was improved when the sodium salt of **20**, prepared *in situ* with sodium hydride[15], was used instead of the potassium salt. In addition, bromination of **18** proved to be selective when it was conducted[16] in dry ethylene glycol or when the acetoxy derivative[15] of the methyl ester **18** was brominated instead of **16**.

Other alkylation methods to construct the 2-substituted cyclopentenone skeleton have also been reported. For example, alkylation of enamine **23** with methyl 6-formyl hexanoate **22**[17,41] provided a direct route to **12** after isomerization of the 2-exo-cyclopentenone **21**.[18] In addition, alkylation of the enediolate **25**, prepared from the enediol-bis-trimethylsilyl ether **26**, with 7-iodoheptanoate[19] afforded the 2-hydroxy cyclopentanone **24**[20] which was transformed to **12** as shown in scheme 8.

With regard to the second approach, for synthesizing **12**, which is based on the base catalysed cyclization of certain γ-dicarbonyl compounds or their equivalents, the number of synthetic methods is enormous, although all are closely related. For example, hydrolysis of the γ-keto acetal **28**[21], and subsequent base catalysed cyclization affords the 2-substituted cyclopentenone **27** which could be used as a PGE_1 precursor or be easily converted to **12**. Similarly, base catalysed cyclizations of the γ-keto aldehydes **29**[22] and **31**[23] lead directly to the 2-substituted cyclopentenones **12** and **30** respectively (scheme 9).



Scheme 8 : Synthetic routes, based on alkylation of cyclopentanone equivalents, for preparing **12**.

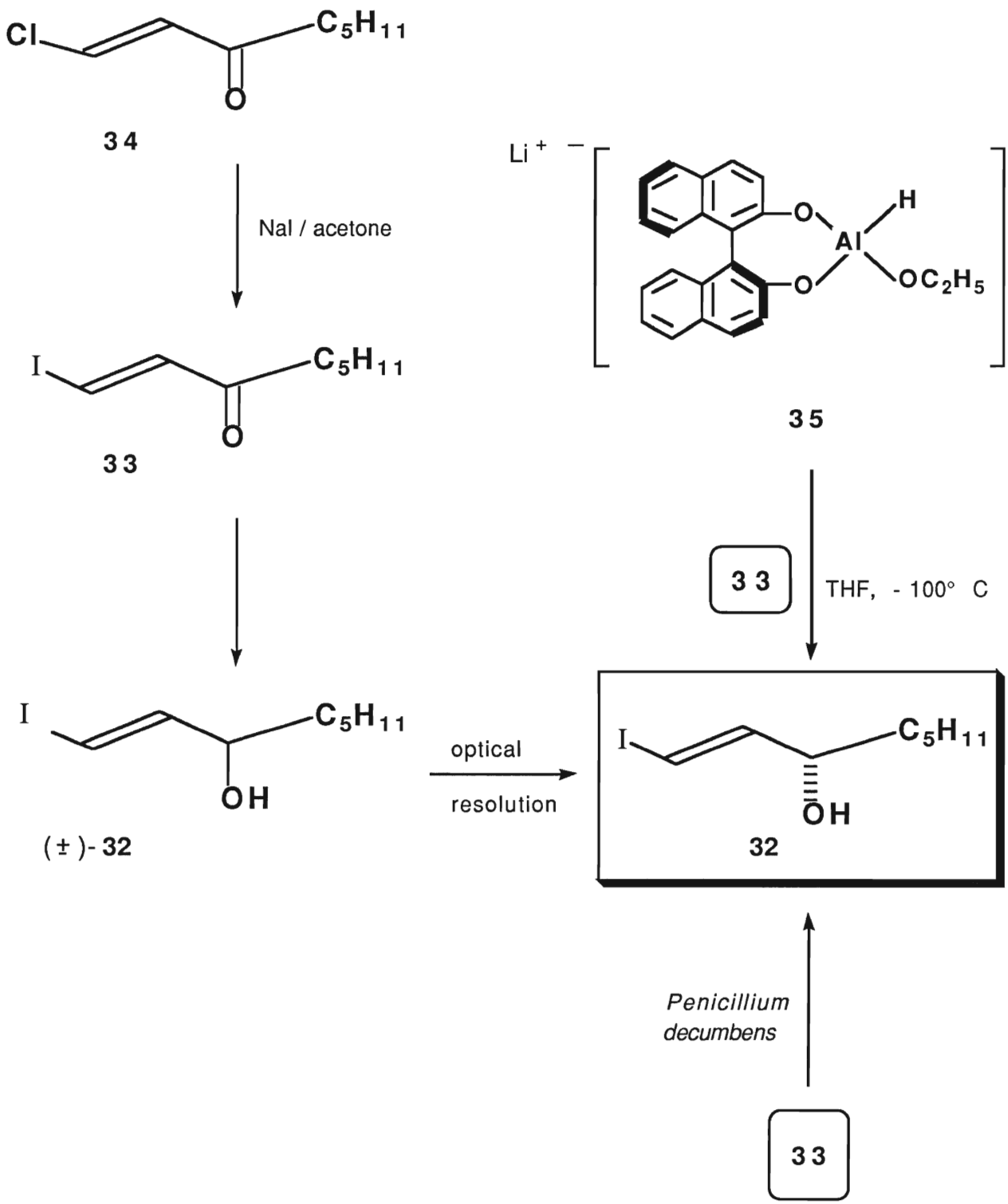


Scheme 9 : Synthetic routes to 2-substituted cyclopentenone **12** based-on base-catalyzed cyclizations of γ- dicarbonyl compounds.

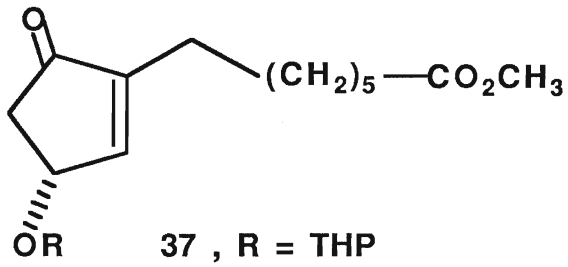
The racemic trans-3-(**S**)-hydroxy-1-iodooctene (±)-**32** having the ω side-chain structure was first prepared by Corey[24] by hydride reduction of the iodovinyl ketone **33** which is available from the chlorovinyl ketone **34**, scheme 10. The required 3-(**S**)-alcohol **32** which carries the right stereochemistry at C-15 of the prostaglandin skeleton (prostaglandin numbering) is obtained by optical resolution[5] of the racemate, or by asymmetric reduction of the corresponding enone using chemical or enzymatic methods (scheme 10). The chemical asymmetric reduction[4] involves the use of the chiral aluminium hydride reagent (BINAL- H), **35**, while the enzymatic reduction was done microbiologically with *Penicillium decumbens* .[4b]

II -1.2. **Synthesis of PGE .**

Organometallic reagents have played an important role in developing many synthetic methodologies to prostaglandins *via* the conjugate addition approach. The construction of PGs *via* the 1,4 addition of organocuprate reagents to α,β-unsaturated ketones was initially developed by Sih[4a] and Fried[5] in 1972. They found that the chiral organocuprate reagent **40** underwent conjugate addition to 2-cyclopenten-1-one to give exclusively the 1,4-addition adduct. Sih and his group later[4b] developed this approach for the synthesis of natural PGE_1. They reported that addition of the chiral cuprate complex **40** , prepared from the organolithium derivative of the ω side-chain, to the optically active cyclopentenone derivative **39** afforded, after deprotection, natural PGE_1 in good yield (scheme 11). This type of conjugate addition has been modified and improved[25]

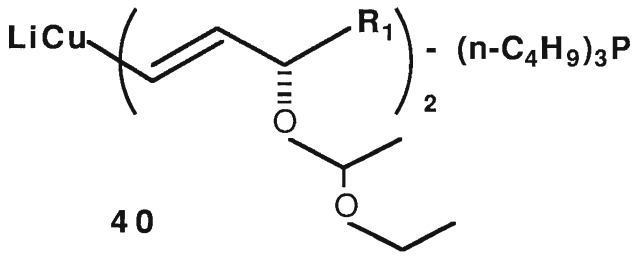


Scheme 10 : Synthetic routes to optically active trans-1-(**S**)-hydroxy-1-iodo-octene, **32**.



37 , R = THP
38 , R = Si $(C_2H_5)_3$
39 , R = Si $(CH_3)_2$ -^{t}Bu

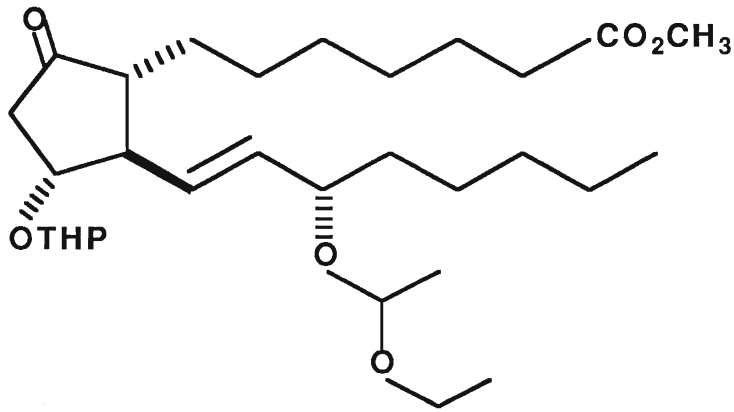
+



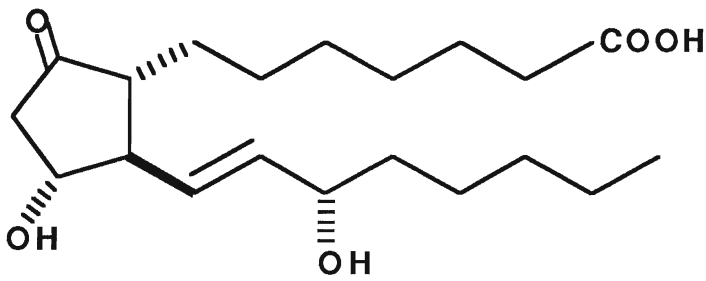
40

R_1 = n-C_5H_{11}

0° C
dry ether



1. H_3O^+
2. *Rhizopus oryzae*



PGE_1

Scheme 11: Synthesis of PGE_1 by conjugate cuprate addition

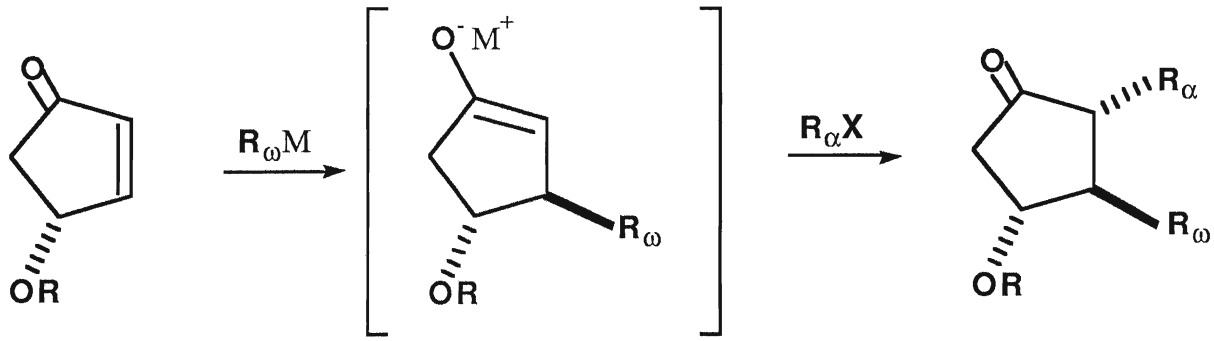
extensively in the past ten years as the search for more selective reagents and catalysts continued.

Weiss and co-workers[9] also developed a novel method for effecting the 1,4-conjugate additions to cyclopentenones using trialkyl-trans-1-alkenylalanates reagents. They reported the synthesis of PGE_1 and congeners via conjugate addition of alanate reagents, carrying the ω side- chain of prostaglandin, to the cyclopentenone derivative (±)-**37**.

II-2. **The three-component conjugate addition method.**

For directness and high flexibility, the three-component coupling process has been developed recently as the shortest and most convenient synthetic route for the preparation of PGs. As the name suggests, the three-component coupling process is a one-pot combination of the cyclopentenone ring and the two side chains to construct the PG skeleton. The synthesis is initiated by a nucleophilic transfer of the ϖ side-chain unit to a protected 4-(**R**)-hydroxy-2-cyclopentenone **41** followed by an electrophilic trapping of the enolate intermediate **42** with α side-chain equivalent ($R_\alpha X$) leading to the required prostaglandin skeleton **43**[26] (scheme 12).

Since organocuprate reagents have been used to deliver organic groups to the β-position of α, β-unsaturated ketones, one might expect that conjugate addition of the ϖ side-chain unit to the 4-hydroxy-2-cyclopentenone followed by alkylation of the resulting enolate with alkyl halides carrying the β side-chain could lead directly to PGs derivatives. However, in reality, such a process is not easy to achieve (see below).



41 **42** **43**

R	is a suitable protecting group
$\mathbf{R_\omega M}$	is the organometallic complex carrying the lower side chain of PG, $\mathbf{R_\omega}$. M = Li , Cu, etc.
$\mathbf{R_\alpha x}$	is the halide carrying the upper side chain of PG, $\mathbf{R_\alpha}$. **X** = I or Br.

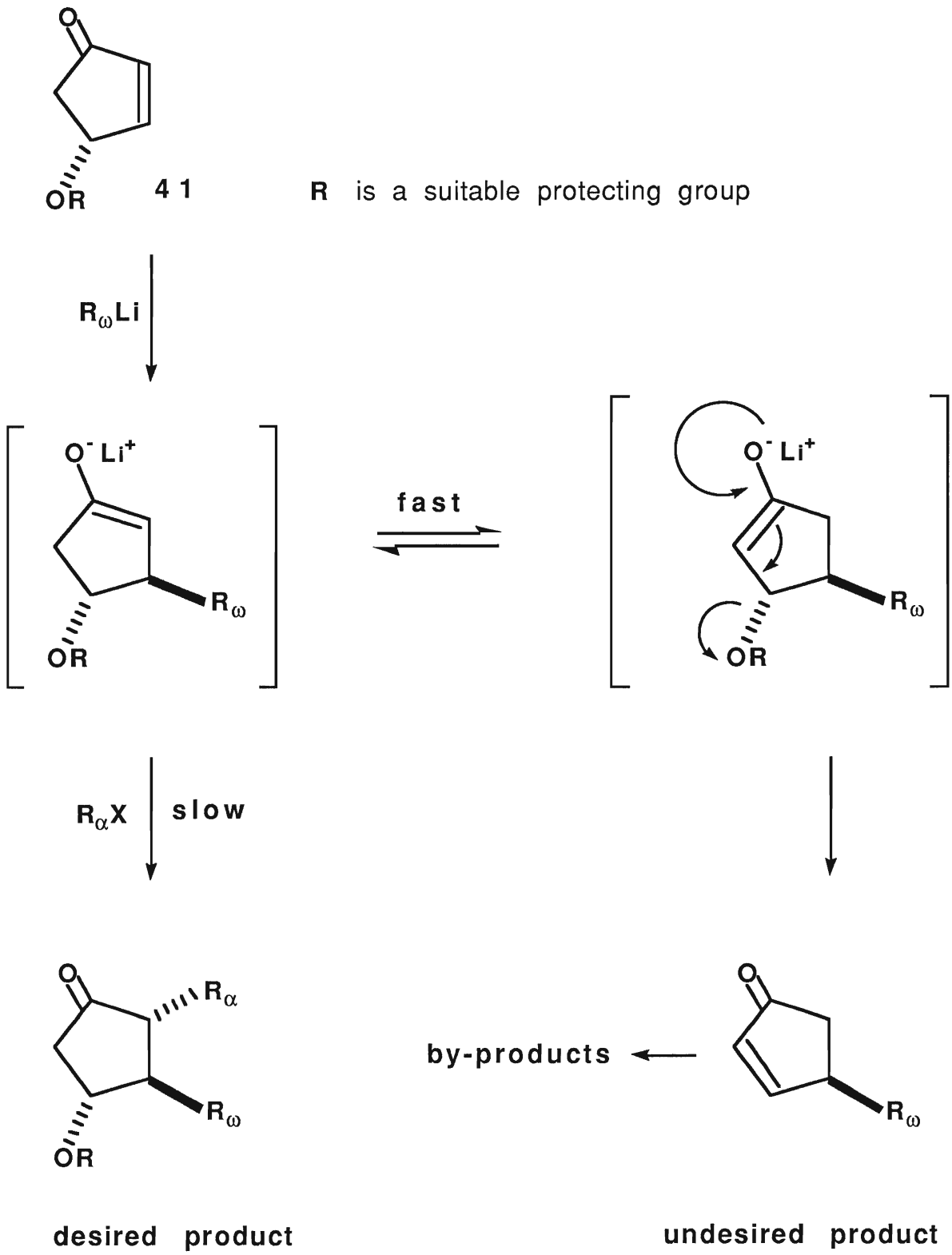
Scheme 12 : Basic strategy of the three-component coupling process.

II - 2.1. **History of the method.**

The idea of conjugate addition followed by enolate trapping was initiated by Patterson and Fried[27] in 1974. They designed several model experiments using 2-cyclopentenones. They reported that conjugate addition of the organocuprate derived from **33** to 2-cyclopentenone followed by reaction with an allyl bromide failed to give the expected product . It was then suggested[28] that the failure of these attempts is presumably attributed to the complex nature of the reaction system.

The lack of organometallic reagents that would facilitate this two carbon-carbon bond construction process limited this ideal route for many years. In 1975 Stock and Isobe[29] realized that the reactivity of the electrophile for trapping the enolate is critical, so they developed a modified and indirect route for the synthesis of $PGF_{2\alpha}$ in 9% yield using formaldehyde as a trapping agent. In 1977, Tanaka and co-workers[30] used acid chlorides to trap the enolates formed from the reaction of enones and cuprate reagent. A PGE_1 derivative, namely, 7-oxo-PGE_1 derivative was obtained using this method.

In view of the above results, it was postulated[31] that the difficulties so far encountered in establishing a direct route to PGs using the three-component coupling process were presumably attributable to a competitive side reaction. It was suggested that a double bond migration of the initially formed enolate (scheme 13) could occur causing dehydration, a process with which the slow alkylation reaction cannot compete. Although the problem was partially solved by using highly reactive electrophiles such as acyl



Scheme 13 : The concept of enolate equilibration during the cuprate addition.

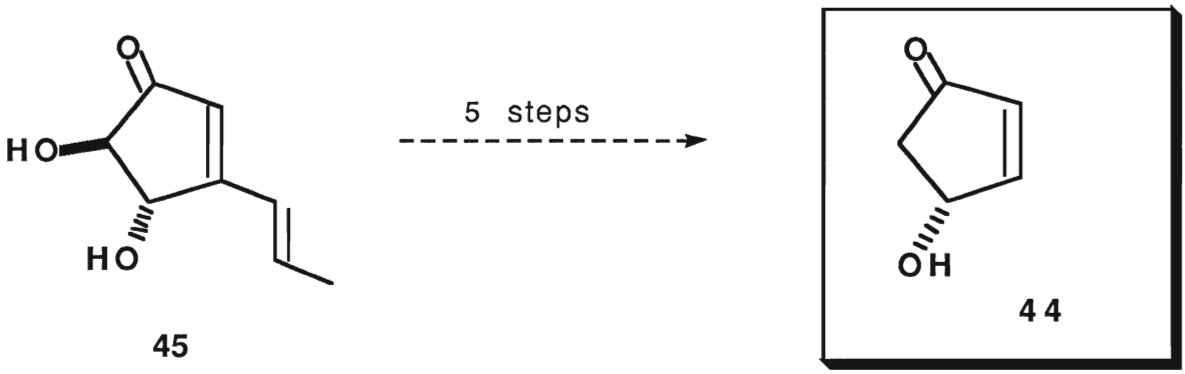
chlorides[30] and strong Michael acceptors[31], the routes were still indirect and the coupling-process definitely needed improvement.

Due to the advantages of the three-component coupling process if it works, the research for finding the required reagents and conditions for the success of this method continued in spite of the discouraging results obtained earlier. The objectives were 1) to be able to create chiral building blocks with the natural (11**R**,15**S**)-configuration, and 2) develop a method which enables the stereospecific combination of the enone unit and the ϖ and α side-chain units in such a way that the trapping of the enolate is fast and efficient.

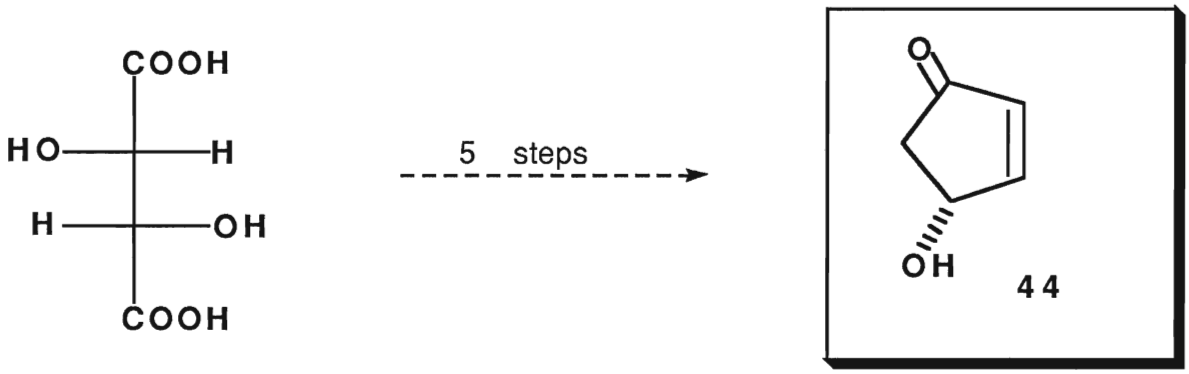
II -2.2. **Access to optically active building Blocks.**

The preparations of the optically active alcohol (S)-**32** which carries the ω side-chain of PG's have already been presented in section II-**1.1**. The optically active cyclopentenone building block **44** can be obtained in various ways (scheme 14). It has been prepared from chiral natural products and *via* resolved synthetic intermediates. For example, Mitscher[32] transformed the naturally occurring terrein **45** in 5 steps to the optically active **44**. Tsuchihashi[33] used D-tartaric acid **46** as a chiral material for the synthesis of **44**. Asymmetric reduction of 4-cyclopentene-1,3-dione **47** with (**S**)-BINAL-H, reagent **35**, gave **44** in 94% ee and 65% chemical yield[34].

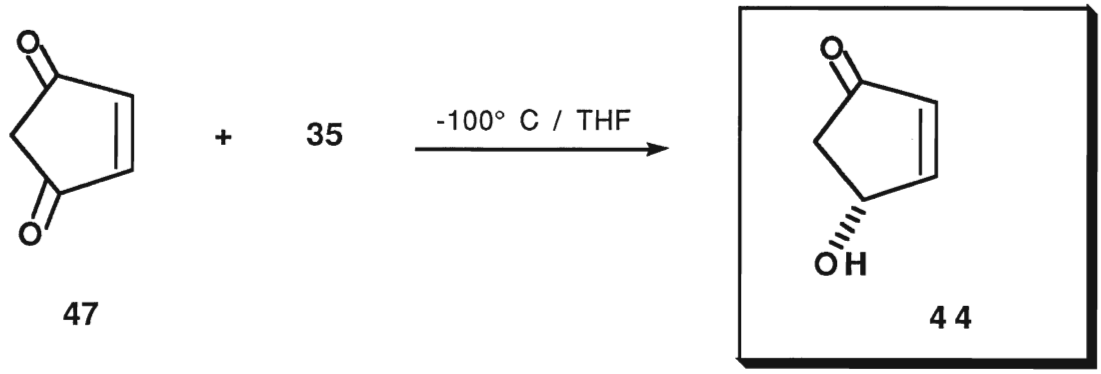
The racemic 4-hydroxy-2-cyclopentenone (±)-**44** could also be prepared by various routes (scheme 15). It is easily obtained from furan derivatives. For example, oxidative dimethoxylation of 2-methylfuran



45 44



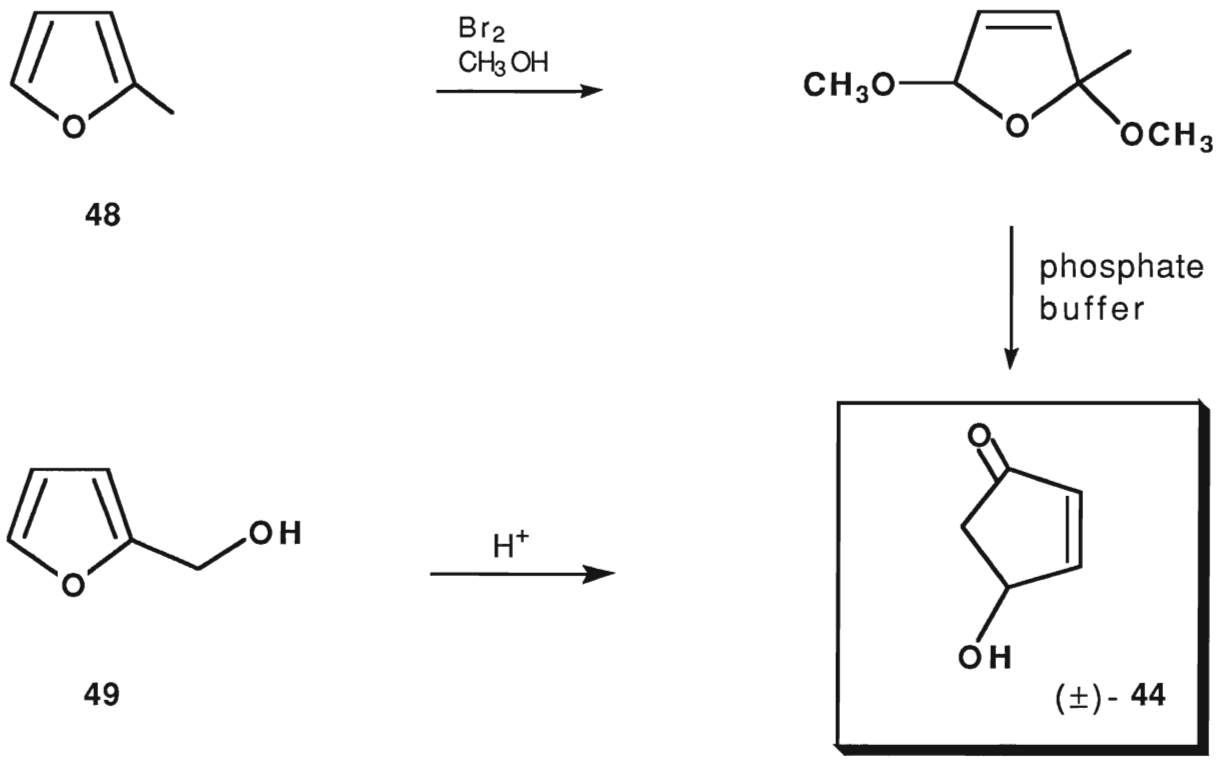
46 44



47 44

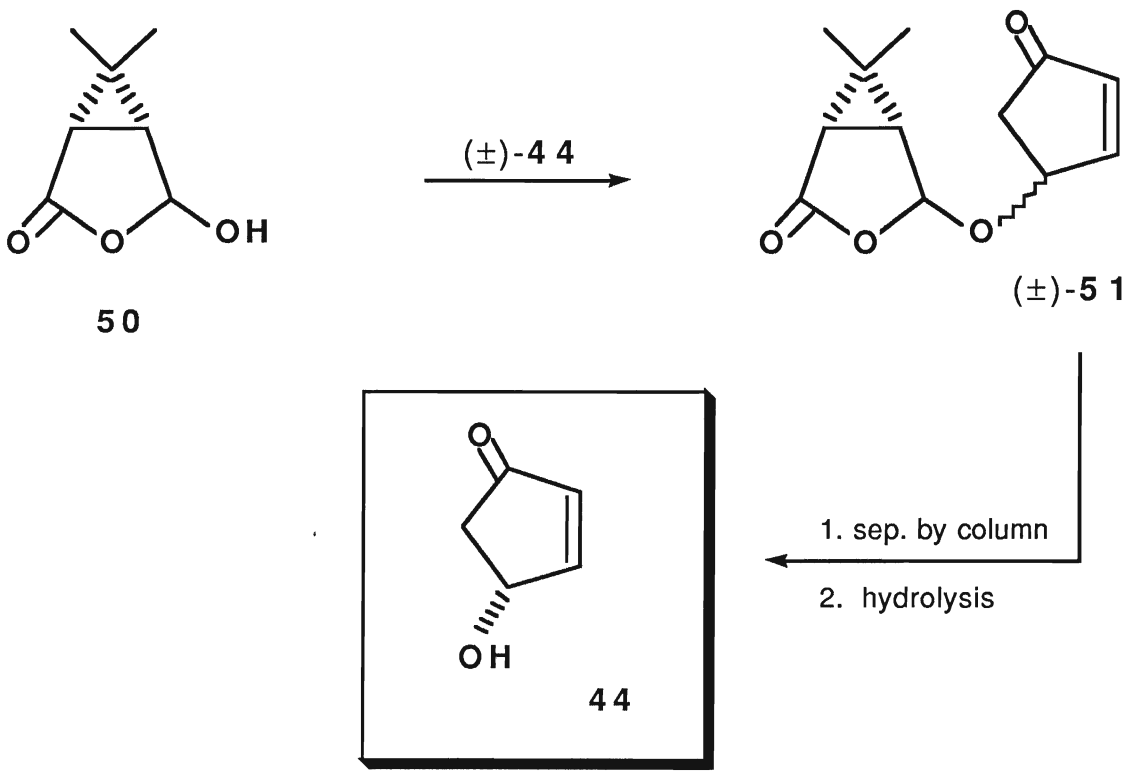
Scheme 14 : Synthetic routes to the optically active (**R**)-4-hydroxy-2-cyclopentenone **44**.

48 with bromine and methanol[35] ,followed by treatment with a phosphate buffer (pH 7.4) afforded (±)-**44** in good yield. This type of rearrangement has recently[36] been modified to afford excellent yields of (±)-**44**. The hydroxyenone could also be produced by simple acid-catalysed rearrangement of 2-furfuryl alcohol **49**[37]. The 4-hydroxyenone (±)-**44** is also accessible from cyclopentadiene[38].



Scheme 15. Synthesis of racemic 4-hydroxy-2-cyclopentenone (±)-**44** .

The hydroxy enone is a rather sensitive compound and its optical resolution by conventional methods is not easy. Recently, however, Noyori and his group[39] found that the bicyclic compound **50** to be an efficient resolving agent. Thus condensation of the racemic hydroxyenone (±)-**44** with **50** gave the diastereomeric adducts **51** which were separated on silica gel column and the more polar fraction hydrolyzed to afford the optically active hydroxy enone **44** in 99% ee and overall yield of 88% based on **50** (scheme 16). Very recently[40], **44** was efficiently prepared in high ee by kinetic resolution of the corresponding racemate (±)-**44** using cationic Rh-BINAP (binaphthyl based phosphine ligand) complexes.



Scheme 16 . Optical resolution of (±)-**44**.

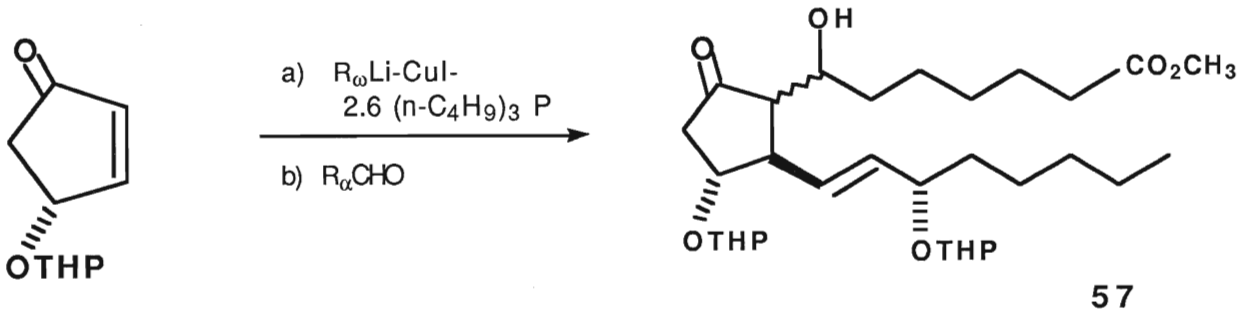
II-2.3. **Development of the method and synthesis of PGE.**

The second objective was to develop a method for the conjugate addition that allows clean enolate trapping which has been the troublesome step in the three-component coupling process. Organometallic reagents have been employed extensively to facilitate such coupling; however, they have to be used in excess in order to ensure the conjugate addition.

When Noyori and his co-workers[25] reinvestigated the use of excess of the ϖ side-chain equivalent, they found that the excess organometallic compound only made the reaction system more complicated. This was rationalized by the fact that if the nucleophile carying the ϖ side-chain is not used in one equivalent, the resulting enolate would not be the only strong nucleophile present in the reaction system. Thus, this would disturb the reaction between the enolate species and the α side-chain electrophile.

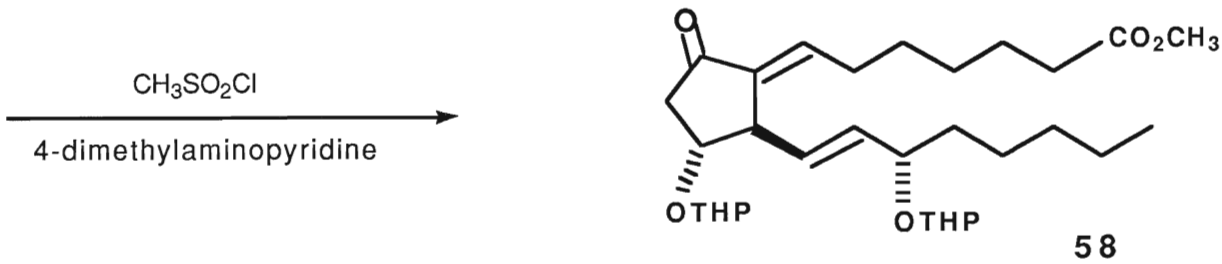
In this context, they prepared the organocopper reagent from equimolar amounts of copper(I) iodide and the organo lithium compound (carrying the ω side-chain) and 2-3 equivalents of tri-n-butylphosphine. When this reagent was allowed to react with 2-cyclopentenone, the conjugate addition product was obtained in high yield. More importantly, the enolate was trapped efficiently with one equivalent of an aldehyde to give the aldol adduct

On these bases, they synthesized PGE_1 in five steps[39,41] via the three-component coupling process which recently[42] came to be known as the Aldol route. The synthesis is illustrated in scheme 17. When the organocopper reagent formed from iodide **55** was

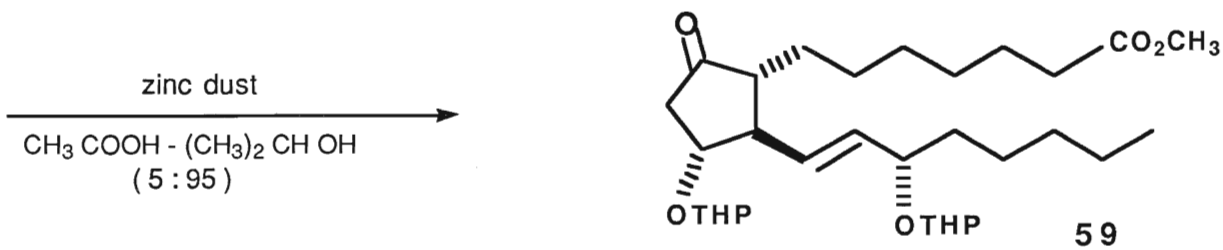


52 , R = THP
53 , R = $Si(C_2H_5)_3$
54 , R = $Si(CH_3)_2$ -^{t}Bu

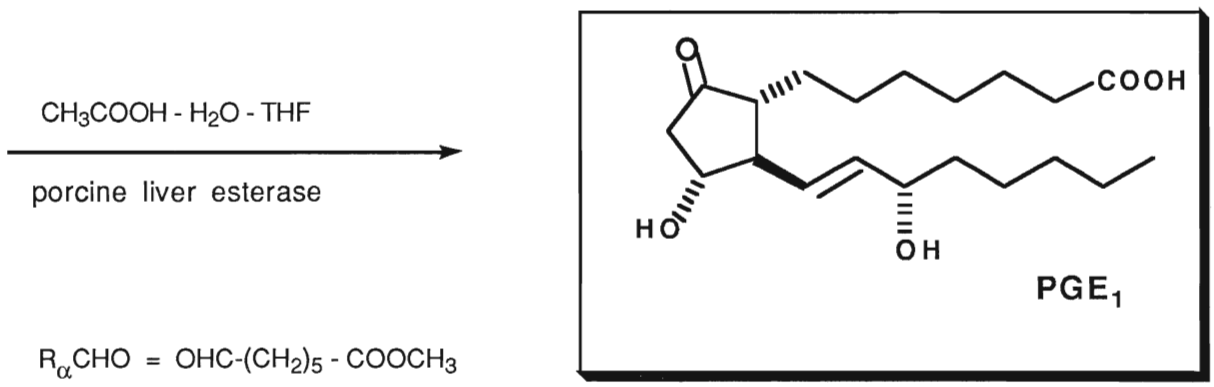
57



58

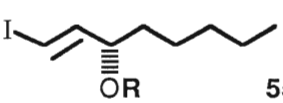


59



PGE_1

$R_\alpha CHO$ = OHC-$(CH_2)_5$ - $COOCH_3$

$R_\omega I$ = 

55 , R = THP
56 , R = Si $(CH_3)_2$ - ^{t}Bu

Scheme 17 . Convergent synthesis of PGE_1 (aldol route).

coupled with the enone **52**, and the resulting enolate was trapped with methyl 6-formylhexanoate, the desired aldol **57** was obtained in 83% yield. Removal of the C-7 hydroxyl group by methanesulfonyl chloride and 4-(dimethylamino) pyridine then gave **58** in 92 % yield. Exposure of **58** to zinc dust in 2-propanol / acetic acid (95 : 5) gave **59** in 84% yield. The yield of **59** was improved to 90% when tributyl tin hydride and di-t-butylperoxide were used. Removal of the tetrahydropyranyl protective groups and subsequent enzymatic hydrolysis of the ester functional group afforded natural PGE_1 in 56% overall yield.

Another, even shorter, synthesis of natural PGE_1 using this three-component coupling process has been reported[43]. The method involved the tandem conjugate addition of the lower side chain equivalent to enone **54** followed by Michael addition of the generated enolate across a nitroolefin carrying the α-side chain to give the expected conjugate addition adduct which was easily transformed to PGE_1.

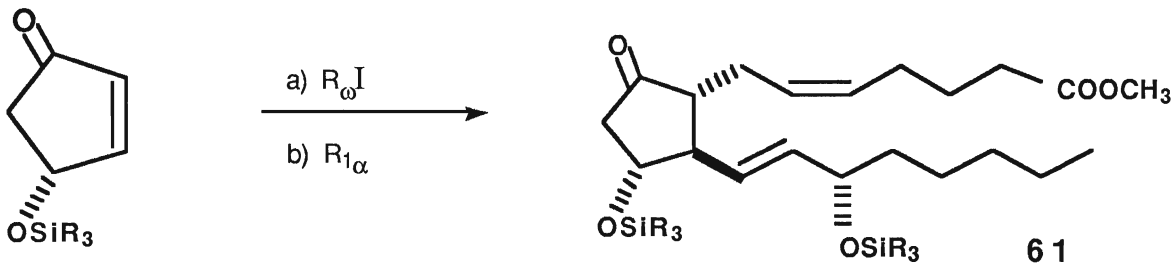
As illustrated in Scheme 17 the four chiral centres of natural PGE_1 are constructed in an efficient way. The absolute configuration at C-11 and C-15 is established at the stage of preparation of starting enone and the ϖ side-chain components. The trans relationship of the three ring-substituents is effected by the conjugate addition of the organo copper reagent and subsequent operations. The trans relationship is favoured kinetically because of steric interactions with the C-11 functionality.

At this stage, it is important to emphasize the point that the

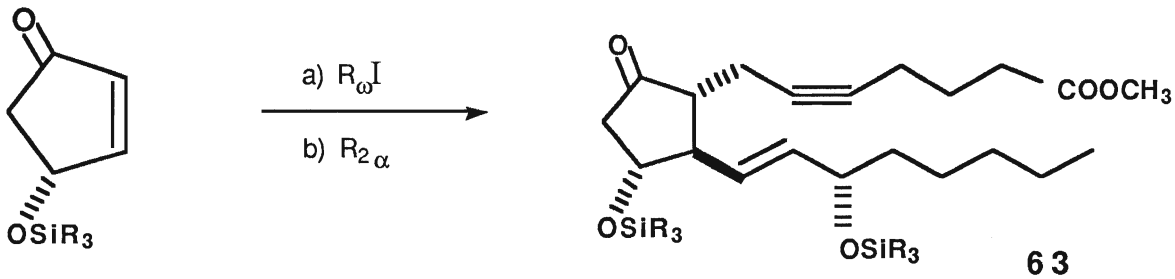
synthesis of (-)-PGE_1 presented above is still considered to be an indirect route for construction of the PGE_1 skeleton. That is to say that although the synthesis employs the three-component coupling process mentioned above, subsequent operations had to be done in order to construct the required PGE_1 derivative **59**.

Recently, a three-step route to PGE_2 was established[26,44] through the tandem conjugate addition/alkylation sequence (scheme 18). The treatment of the enone **54** with the organocopper reagent, prepared[25] from **56** in the presence of hexamethyl phosphoric triamide (HMPA) and triphenyltin chloride, followed by addition of Z-allylic iodide **60** afforded the PGE_2 derivative **61** in 78% yield. This was a single-pot preparation. Natural PGE_2 is then obtained by removal of the protecting groups.

When this three-component coupling is done with the proparyglic iodide **62**, the 5,6-dehydro-PGE_2 derivative **63** is produced. Compound **63** serves as a common intermediate for the synthesis of some naturally occuring PGs. For example, partial hydrogenation of the 5,6 triple bond could be done over 5% $Pd/BaSO_4$ catalyst to give PGE_2. Unfortunately the above direct approaches do not work for the construction of PGE_1 skeleton because a reactive α side-chain equivalents such as **60** or **62** would be needed to achieve efficient enolate trapping . Recently, the discovery[45] that dimethyl zinc was found to enhance the alkylation of lithium enolates improved this triply convergent synthesis.

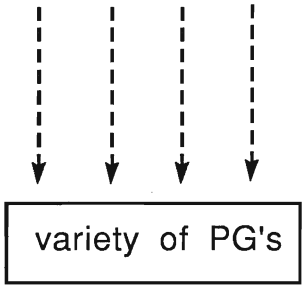


54 **61**

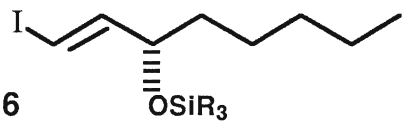


54 **63**

SiR_3 = $Si(CH_3)_2$ - t-C_4H_9



$R_\omega I$ =



56

$R_{1\alpha}$ =

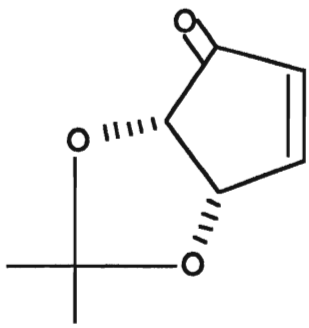
60

$R_{2\alpha}$ =

62

Scheme 18 : Direct three component coupling process for the synthesis of the **PGE_2** derivative **61** and the 5,6-dehydro-**PGE_2** derivative **63**.

Johnson and Penning succeeded [46] in eliminating the equilibration of the enolate resulting from the conjugate addition of the ϖ side-chain to the enone in the three component coupling process (scheme 13). They postulated that enolate equilibration would be suppressed in the presence of α-oxygen functionality constrained in the five membered ring. This requirement was satisfied by the enone **64** which was prepared in six steps in 40% yield from cyclopentadiene. When the conjugate addition was carried out, the trapping of enolate and subsequent alkylation went cleanly to afford the expected conjugate addition/ enolate trapping adduct in excellent yield.



64

All the discussion above has dealt with PGE_1 and PGE_2 and nothing has been said concerning PGE_3. This was done intentionally because most of the literature work has been done on PGE_1 and PGE_2. PGE_3 is actually a PGE_2 analogue in which there is additional cis-double bond between C-17 and C-18 (see scheme 2). Therefore most of the chemistry presented above should apply for PGE_3. The difficulty in synthesizing PGE_3 lies in the synthesis of the lower (ϖ) side-chain with the extra double bond. Recently, Okamoto and co-workers[47] developed a highly efficient synthesis of natural PGE_3.

II-3. **Biological activities of Prostaglandins.**

Prostaglandins exhibit a wide range of biological activity. Prostaglandins of the E type have been shown to inhibit gastric acid secretion in animals. They also lower blood pressure in a variety of species including humans. The actions of the three classes of the PGEs sometimes differ. For example, whereas PGE_1 is a potent inhibitor of platelet aggregation, PGE_2 is not. The E-series prostaglandins also exhibit a powerful action on the uterus.

III - **Synthesis and Biological Activities of PGE Analogs Bearing Modified Side Chains.**

Much of the prostaglandin research in the past two decades has been directed towards the synthesis of modified analogues which might posses greater tissue selectivity and longer duration times in their biological actions than natural prostaglandins.

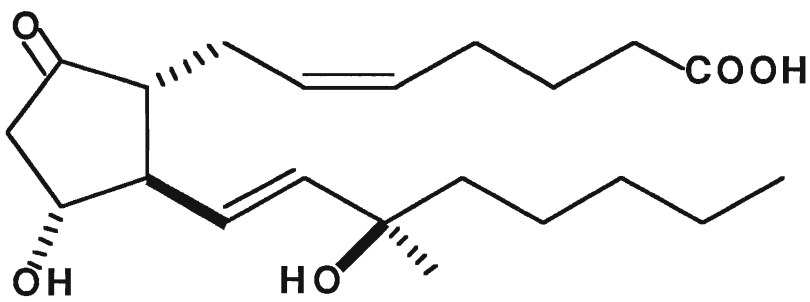
Because only a few of those important and well described analogues will be covered, this section is not a comprehensive survey of all published analogues. Specifically this section will deal only with a few examples of those important analogues of the E-series prostaglandins bearing modified side chains (analogs with modified ring systems have also been prepared) which have been prepared by conjugate addition methods.

III-1. **PGE analogs bearing modified side chains.**

15-Methyl substituted analogues have been prepared and their clinical behaviour has been studied extensively. The interest in these analogues came about as a result of the discovery that the

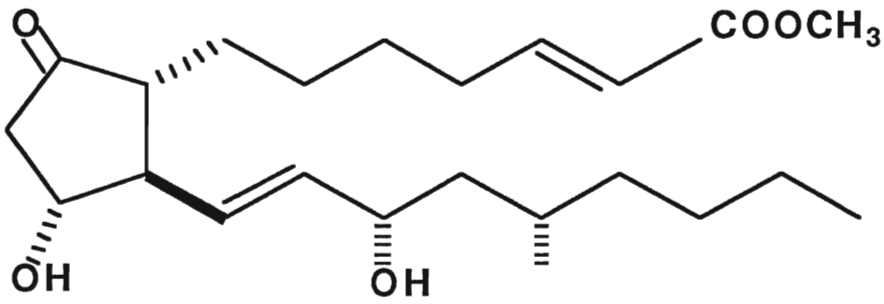
initial step in the metabolism of natural prostaglandins involves oxidation of the C-15 hydroxyl group by the enzyme 15-hydroxyprostaglandin dehydrogenase.[2]

The synthesis of (15**R**)-15-methyl-PGE_2 **65** from $PGF_2\alpha$ is straightforward and has been reported[1]. This analogue has also been prepared by the three-component coupling process.[48] Compound **65** is used in treating patients with gastric ulcers.[2]



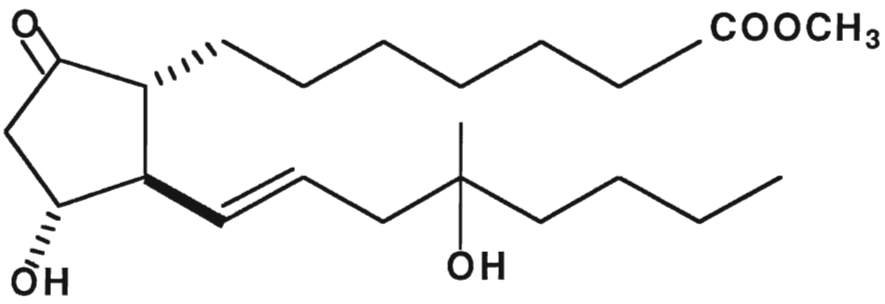
65

The physiologically important analog **66** has also been prepared and clinically tested. Clinical tests showed that **66** decreases blood pressure and hence it has been used in the treatment of some peripheral circulatory disorders and heart diseases.[49]



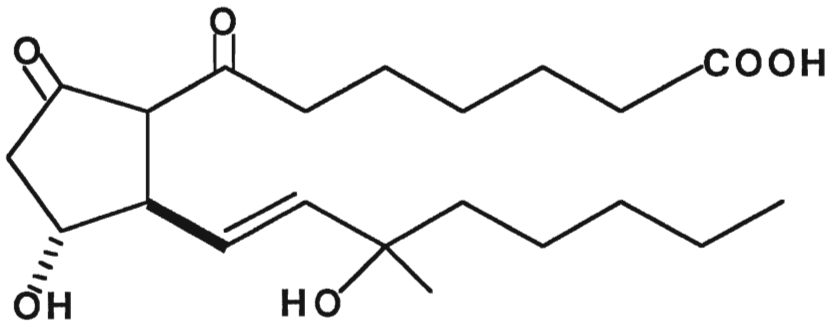
66

The PGE_1 analog **67** which has a hydroxy group in the C-16 position (prostaglandin numbering) was found[50] to have a better gastric antisecretory action than natural PGE_1. This pharmacologically important analog has been traditionally made by the two component coupling process mentioned above using vinylcuprate reagents[51]. Recently, however, two-component conjugate additions using a mixture of vinyl stannanes[52] or vinylzirconates[53] (carrying the required ω side-chain) and higher order cyanocuprates to enone derivatives such as **38** were found to be the best routes to **67** and other analogs with modified side chains.



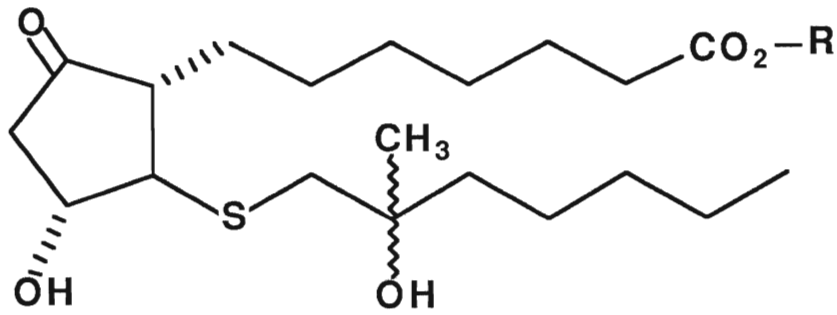
67

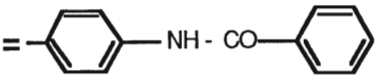
The 15-methyl-7-oxo-PGE_1 derivative **68** has been found to exhibit double the anti-ulcer activity of PGE_2. This analog could be prepared easily via the triply convergent synthesis described above (section II-**2**) using an acid chloride as the α-side chain unit to trap the generated enolate.[30]

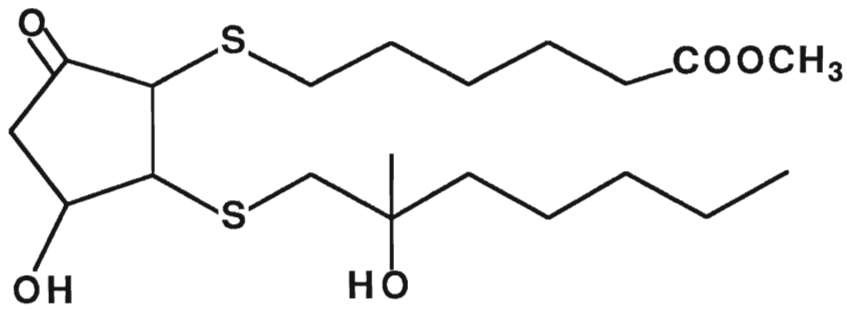


68

Finally, wide varieties of PGE analogs incorporating a heteroatom in one of the side chains have been reported. For example the 13-thia analogs **69** and the 7,13-dithia analog **70** have been prepared and biologically tested. Analog **69** which has been prepared[54] *via* the two-component conjugate addition approach was found to exert inhibition of basal gastric acid output.[54a] Analog **70** whose synthesis[55] also employed the conjugate addition approach was reported to have gastric anti-ulcer activity.



69 , R = 



70

Thia-PGE$_1$ analogs

RESEARCH PROPOSAL.

In view of this exciting and rapidly growing research, we planned for the synthesis of a 15-thia analog of prostaglandin E_1. This 15-thia PGE_1 analog, compound **71**, has never been prepared before and our initial proposal was based on the following interests :

1 - This new compound, if prepared, should be structurally interesting.

2 - More importantly, this closely related PGE_1 analog is likely to be biologically active.

Our choice of replacing the C-15 carbon atom of the natural PGE_1 with a sulphur atom to generate analog **71** was also based on the followings reasons:

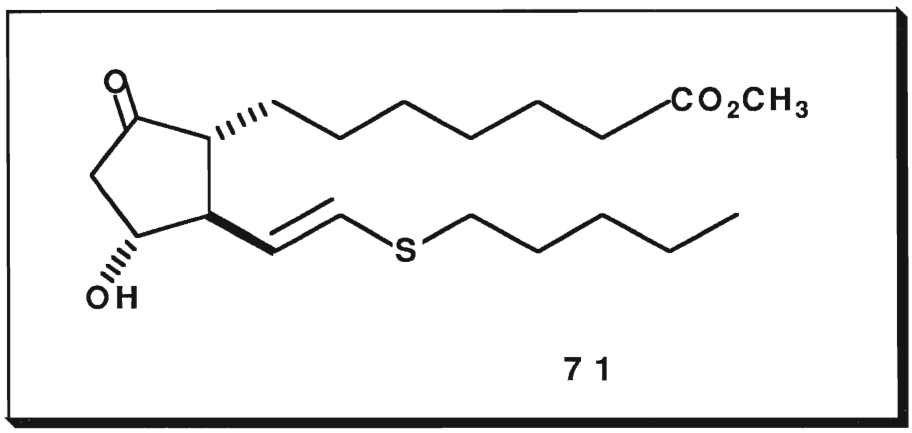
1 - Certain natural product analogs incorporating a sulphur atom (or a sulfoxide group) in place of a secondary alcohol have been shown to be good candidates for enzyme inhibition.

2 - The electronegativity of sulphur is very similar to that of carbon.

3 - Compound **71** is likely to be sulfoxidized in a biological system generating a more stable sulfoxide derivative **72** which may have an even higher biological activity than **71**.

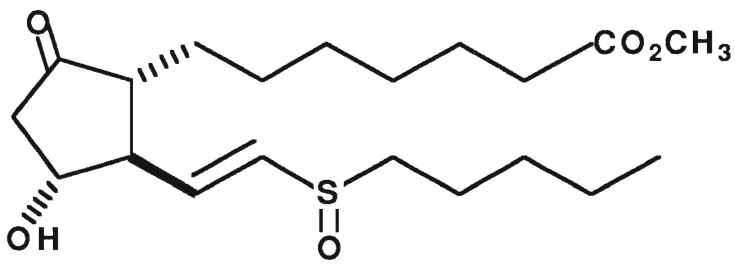
4 - Compound 72 carries an additional chiral center

(the sulphur atom). Since enzymatic sulfoxidation is likely to be stereospecific, it is possible to generate the same absolute stereochemistry at the sulphur atom (S-configuration) as that present at C-15 in the.natural PGE_1. This is likely to contribute to the biological activity of **72**.



71

sulfoxidation



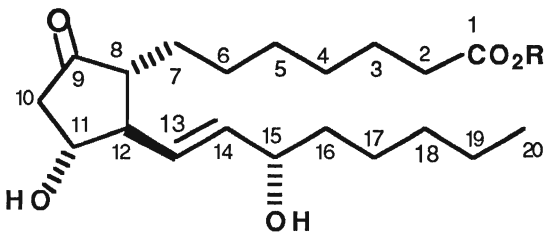
72

DISCUSSION

I- THE SYNTHETIC PLAN :

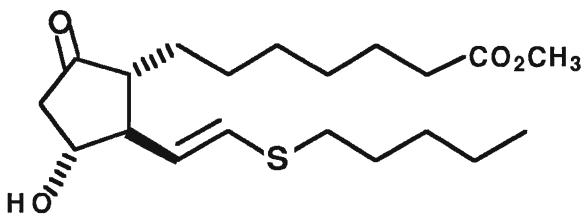
The synthetic plan of the target compound **A** was based on a conjugate addition approach. Therefore, the obvious retrosynthetic route illustrated in scheme 19 revealed that two building blocks such as **A** and **B** are to be prepared then coupled in a controlled fashion to generate the target molecule. The target synthon **A** possesses the cyclopentanone moiety carrying the upper side-chain (α side-chain), while synthon **B** is an equivalent of the lower side-chain (ω side-chain) of the target compound. The latter synthon seemed more likely to be accessible from the acetylenic sulfide **D** probably via an intermediate such as the iodovinyl sulfide **C.**

The target compound **71** is a methyl ester PGE_1 analog. The difference is the replacement of the (CHOH) group in the natural PGE_1 with a sulphur atom in the C-15 position. Regarding the sterochemistry on the ring, compound **71** must possess the trans relationship.

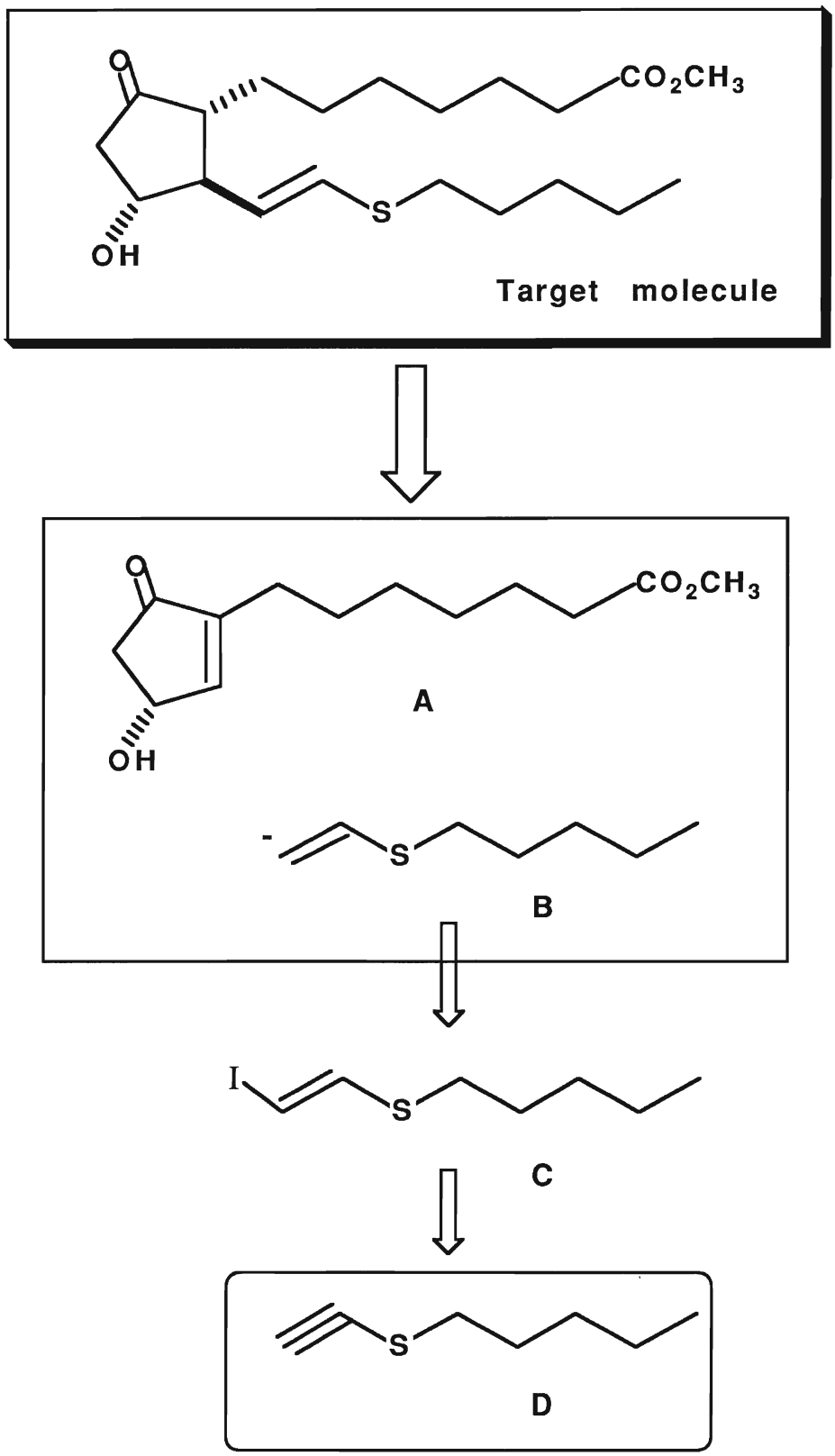


R = H , PGE_1

R = CH_3 , PGE_1 , methyl ester



Target compound **71**



Scheme 19. A retrosynthetic route (based on 1,4-conjugate addition) to the target molecule **71**.

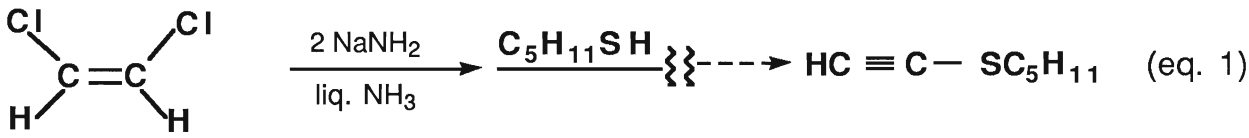
II- Preparation of the lower side-chain equivalents :

I.1 – Preparation of ethynyl n.pentyl sulfide 81.

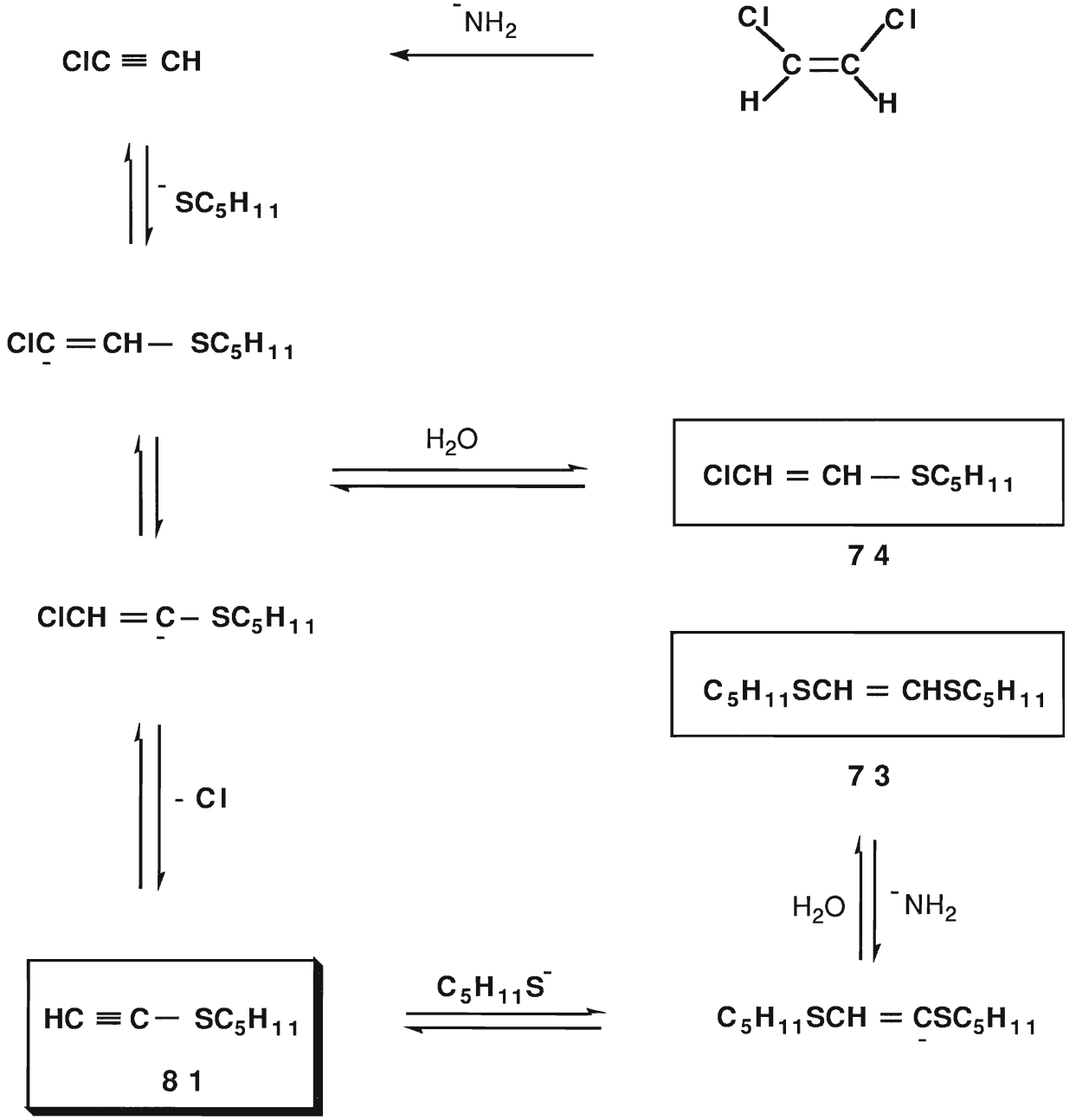
Acetylenic thioethers of the type **HC≡C–SR** (**R** = alkyl) were not known prior to 1956, but at that time four independent reports were issued approximately simultaneously.[56-59] These compounds are considered versatile organic intermediates and our interest in them stemmed from the fact that we required multi-gram quantities of the alkynylthioether ethynyl n-pentylsufide and the E isomer of the corresponding iodoethenyl thioether.

In searching for the most convenient and efficient method for the synthesis of ethynyl n-pentyl sulfide, we investigated several approaches, some of which have been reported to be successful for the preparation of similar compounds. Because we required the title compound to be used in the total synthesis of the 15 -thia prostaglandin analogs, we initially looked at the shortest route to synthesize it.

In this respect, we attempted the preparation of **81** by a one-stage synthesis from cis-1,2-dichloroethylene and one equivalent of pentylthiol (equation 1, scheme 20). Although t-butyl ethynyl sulfide can be obtained in low yield from Z-1,2-dichloro ethylene and t-butyl-mercaptan[60], this procedure did not give any of the desired acetylenic product when n.pentylmercaptan was used as the thiol reagent. Instead we obtained cis-1,2-bis-(pentylthio) ethylene **73** in 25% yield along with cis-1-pentylthio-2-chloroethylene **74** in 10% yield. IR analysis of the crude product showed only small traces of the desired acetylene thioether.



(eq. 1)



Scheme **20**. An attempted synthesis of **81** using an addition - elimination method and some of the equilibria that could exist in the reaction.

These somewhat disappointing results are explicable if one considers the complex nature of the reaction. It is probably due to the many equilibria (scheme 20) present in the reaction mixture that the desired acelylenic thioether, which seems to be an intermediate product in the mechanism resulting in cis-1,2-bis-(pentylthio) ethylene, could not be isolated under these conditions.

Secondly, we looked into another one-stage synthesis. This procedure (eq. 2) involved a thiolation-alkylation sequence of a lithium acetylenide equivalent, namely, the lithium acetylenide ethylene-diamine complex **75**.[61] Thus, alkylation of the alkyne-thiolate **76** prepared from **75** and S_8 with pentyl iodide or bromide should in theory give the desired acetylene thioether **81**.

However, in spite of the extensive experimentation with this procedure, the results were unsatisfactory. Generally, the results (table **1**) seem to indicate that the alkylation is very slow and sluggish. It also seems that the rate of alkylation increases as the polarity of the solvent used increases. For example, when carrying out the experiment in THF the desired alkylation was not observed whereas when the highly polar liquid ammonia was used as solvent, relatively moderate yields of the desired alkyne were obtained. When using DMSO as the solvent some alkylation took place but this was hampered by side reactions.

The undesired products obtained (see table **1**) also suggested that the thiolation step is not very efficient at high temperatures (8° C). It seemed that carrying out the thiolation at low temperatures had a beneficial effect in repressing the undesired side reactions. Thus, when the thiolation was carried out at - 40° C,

$$HC\equiv CLi \cdot H_2N(CH_2)_2NH_2 \xrightarrow[\text{solvent, time}_1\text{, temp}_1{}^{a}.]{S_8} HC\equiv CS^-Li^+ \xrightarrow[\text{time}_2\text{, temp}_2{}^{b}.]{C_5H_{11}-X} HC\equiv C-SC_5H_{11} \quad \text{(eq. 2)}$$

75 **76** **81**

Table 1. Results from the thiolation-alkylation methods (reaction above) attempted to prepare the acetylene thioether **81.**

solvent	$time_1$	$temp_1$	$time_2$	$temp_2$	X	% yield of **81**	by-products
THF	1 hr	8 ° to RT	2 hr	8 ° to RT	I	zero	$C_5H_{11}S\text{-}SC_5H_{11}$ + $C_5H_{11}\text{-}S\text{-}S\text{-}S\text{-}C_5H_{11}$
DMSO	1 hr	8 ° to RT	"	"	I	zero	
THF	1 hr	8 ° to RT	6 hr	8 ° to RT	I	zero	
DMSO	1 hr	8 ° to RT	"	"	I	5 %	
liq. NH_3	15 min	- 40 °	4 hr	- 35 °	I	24 %	
liq. NH_3	15 min	- 40 °	"	"	Br	18 %	

[a] $time_1$ and $temp_1$ refer to the reaction's time and temperature of the thiolation step (**75** → **76**).

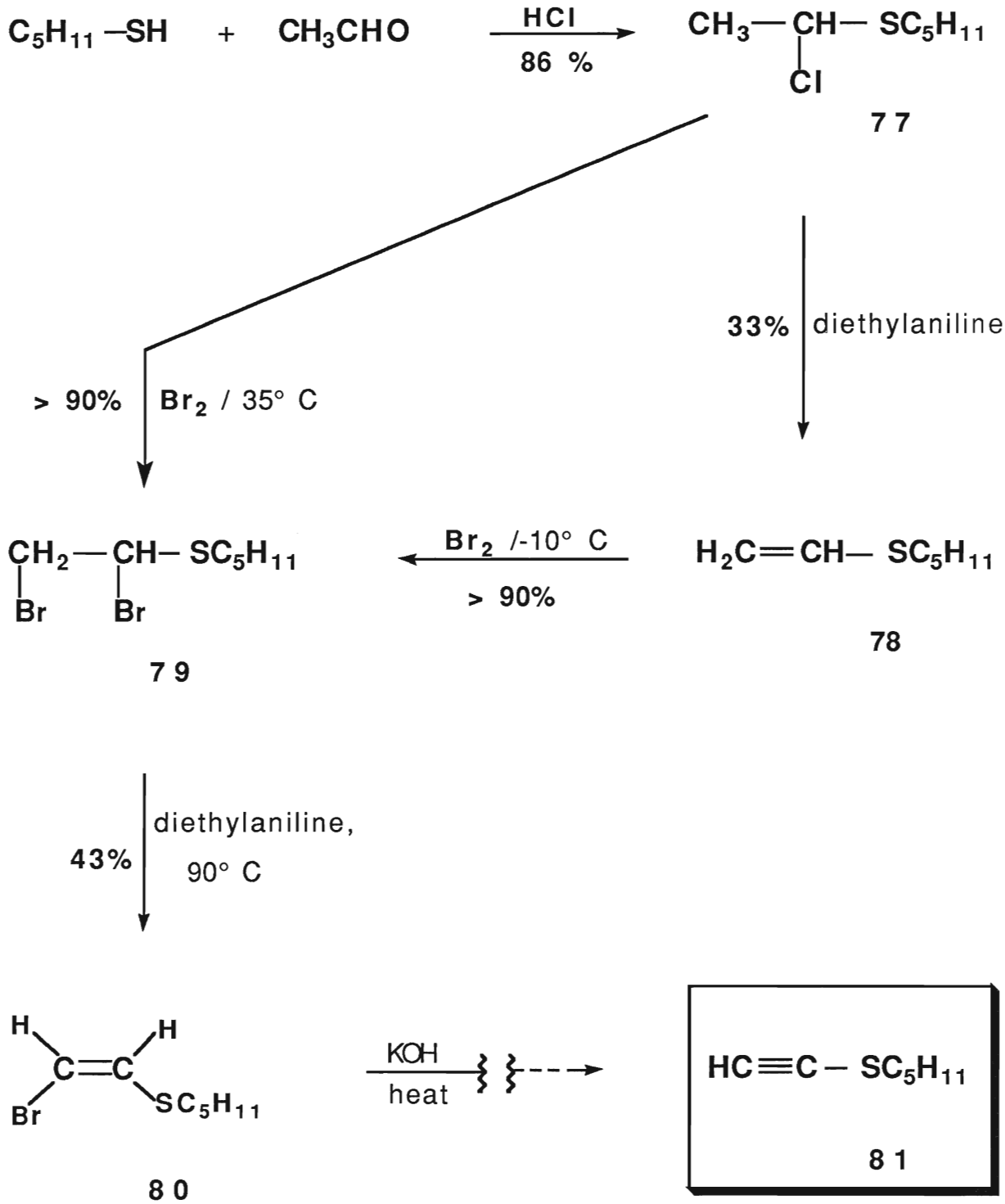
[b] $time_2$ and $temp_2$ refer to the reaction's time and temperature of the alkylation step (**76** → **81**).

subsequent alkylation produced the desired acetylenic sulfide and only the starting material (the alkylhalide) which remained unalkylated.

The formation of the dialkyl disulfides and trisulfides in the reaction with the other two solvents (THF and DMSO) may suggest that at relatively high temperatures the chain of sulphur atoms is not cleaved in a controlled way.

Next, we looked into a multi-step approach[59] for the synthesis of **81**. In particular, we wanted to consider some methods which are based on eliminations since these reactions are commonly used for the introduction of triple bonds. Thus, we investigated scheme 21 in which methods were somewhat successful for the preparation of t-butyl ethynyl sulfide and ethyl ethynyl sulfide .

Applying the general method shown in scheme 21, we successfully prepared 1-chloroethyl n.pentyl sulfide **77** from acetaldehyde and one equivalent of n-pentylthiol in the presence of a large excess of hydrogen chloride. The preparation of these α – chloro-thio ethers by this method is often hampered by side reactions such as the condensation of the aldehyde and the formation of considerable amounts of thioacetals.[59] In our case, we did not detect any aldol condensation products, possibly because we conducted the experiment at low temperatures throughout the entire introduction of hydrogen chloride. Regarding the formation of the thioacetal, we only obtained small amounts and the desired chlorothioether **77** was formed in excellent yield (86%).



Scheme 21. An elimination method attempted for the preparation of alkyne **81**.

The chlorothioether **77** could then be converted to 1,2-dibromoethyl n.pentyl sulfide **79** by bromination of the isolated intermediate ethylene n.pentyl sulfide **78**. The conversion of α-chlorothioethers with short alkyl chains to vinyl sulfides is a known reaction. In our case, only 33 % of the vinyl sulfide **78** was obtained when the chlorothioether **77** was treated with diethylaniline (see scheme 21) which of course resulted in an overall reduction in the yield of the desired dibromothioether **79**.

Our approach to the preparation of 1,2-dibromoethyl n.pentyl sulfide **79** involved the direct bromination of the α-chloro thioether **77** at 35° C. It was essential that the internal temperature of the reaction mixture be kept below 35° C, otherwise uncontrolled dehydrohalogenation would take place. We envisage that the formation of the 1,2-dibromo-thioether **79** appears to be best accounted for by proposing dehydro-chlorination of the α-chloroethyl sulfide **77** followed by the addition of bromine which probably acts as a base in the dehydrochlorination step.

Purification of the dibromide **79** was not attempted because of its suspected instability. Therefore, it was treated immediately with freshly distiled diethylaniline. The resulting 2- bromoethyl n.pentyl sulfide **80** was purified by distillation in vacuo. ^1H nmr analysis of the product confirmed that it is predominantly (90 %) the Z-isomer based on a J value for the olefinic hydrogens.

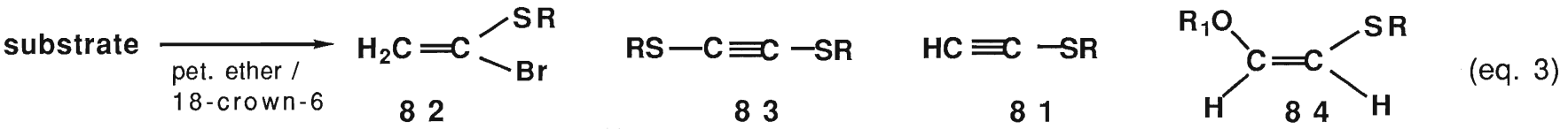
Of course, for our synthetic purposes, getting the Z-isomer was not useful to us since we were seeking the E-isomer which we initially planned to prepare from the acetylenic thioether **81**. Nevertheless, we subjected the bromovinyl thioether **80** to dehydro-

bromination using powdered potassium hydroxide hoping to get the desired acetylenic thioether **81**. However, this only resulted in the recovery of starting material and some high boiling unidentified residue. Therefore, we had to modify scheme 21, specifically, at the dehydrohalogenation step, that is, the reaction leading to **81** from **79**. In this respect, we thought of subjecting **79** to some type of a base where double dehydrohalogenation may be possible.

Based on a report by Dehmlow[62] in which he had developed a method for the rapid formation of alkynes from vicinal dibromides using powdered potassium hydroxide and catalytic amounts of lipophilic transfer catalysts, we attempted a double dehydrobromination on the dibromide using this phase transfer catalysis (PTC) method. Thus, when a solution of **79** and catalytic amount of 18-crown-6 in petroleum ether (b.p. 35-57° C) was added to 2 equivalents of powdered potassium hydroxide and the mixture was refluxed, 1-bromovinyl n-pentyl sulfide **82** was obtained as the main product (eq. 3). When we tried to force the double dehydrohalogenation by using a solvent with a higher boiling point, the bromovinyl sulfide **82** was again obtained as the major product and we also isolated a small amount of the bis-pentylthioalkyne **83** The latter compound was also obtained when we attempted the dehydro-bromination of the isolated bromovinyl sulfide under similar conditions (see table **2**).

The above results suggested to us two facts:

1) A stronger base is undoubtedly required to furnish the double dehydrobromination of **79**, and



(eq. 3)

$R = C_5H_{11}$
$R_1 = C(CH_3)_3$

Table 2. Results from Phase Transfer Catalysis methods attempted for preparing the acetylenic thioether **81**.

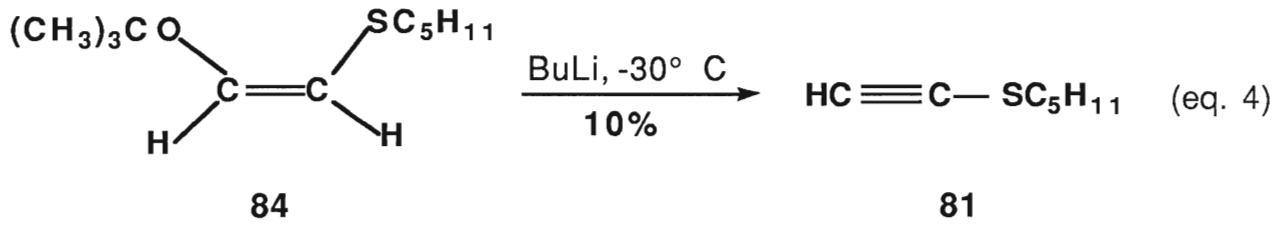
entry	substrate	base	amount of base	time (hr)	temp(°C)	% yield[a] 82	83	81	84
1	$CH_2(Br)-CH(Br)-SR$	KOH	2 EQ	9	45	20	6	5	
2	"	KOH	2.5 EQ	9	90	40	25	0	
3	$H_2C=C(SR)Br$	KOH	2 EQ	5	90	36	17		
4	$CH_2(Br)-CH(Br)-SR$	t-BuOK	2 EQ	2	90			10	
5	"	"	2 EQ	4	90			22	10
6	"	"	2 EQ	7	90			5	20
7	"	"	3 EQ	7	90			4	45

[a] % yields are of purified materials

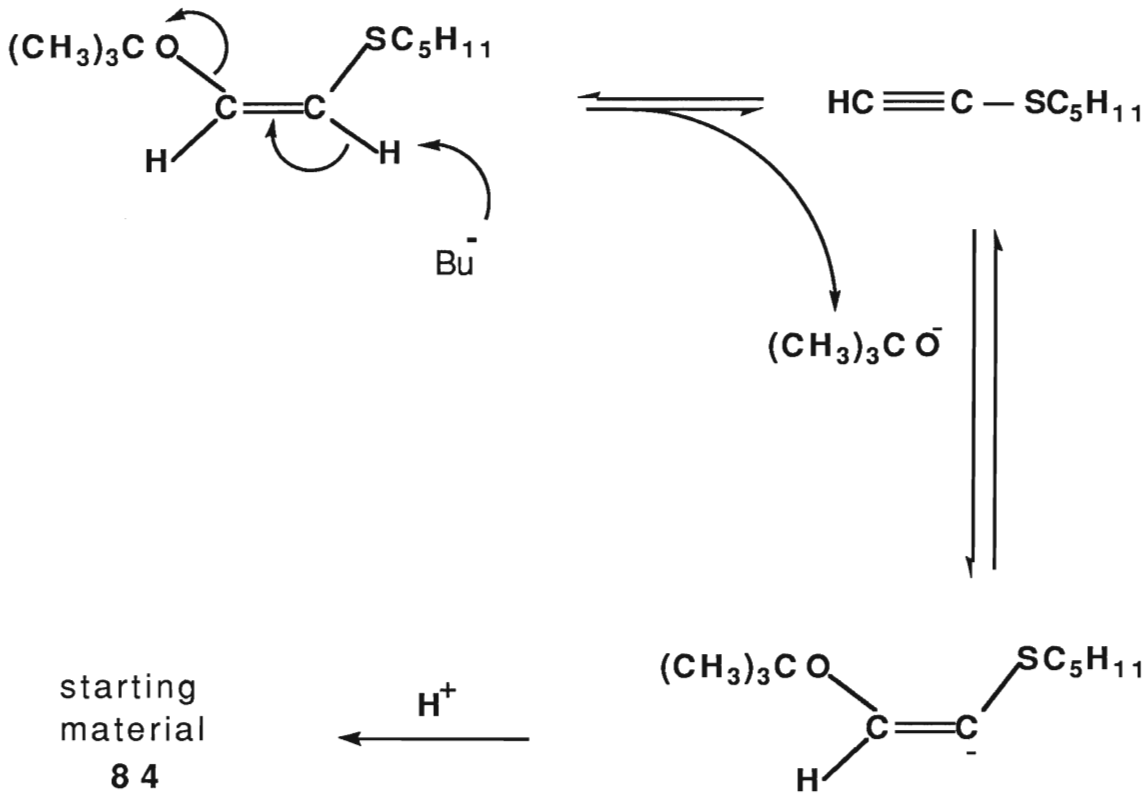
2) Milder reaction conditions are most likely to be used for such dehydrohalogenation.

Considering the first idea, we thought of using potassium t-butoxide as the base in a PTC experiment similar to the one mentioned above. This method resulted in the formation of the desired product **81** in a maximum yield of 22% after distillation. In an attempt to improve the yield of **81** we varied the reaction periods and amount of base used (table **2**) but without success. In fact, it appeared to us that the major and reproducible product was actually (Z)-1-t-butoxy-2-pentylthio-ethene **84** which we assumed is resulting from the addition of the t-butoxide ion to the presumably formed acetylene **81**. This was confirmed latter on by an actual experiment in which the acetylenic thioether **81** was allowed to react with potassium t-butoxide under the same conditions to form (Z)-1-t-butoxy-2-pentylthioethene **84**.

The latter compound was treated with butyllithium in an attempt to eliminate the tertiary alkoxide and form the alkyne **81**. The elimination did proceed although not in satisfactory fashion. The low percentage yield obtained probably suggests the need to remove the alcoholate before working up. In other words, the recovery of large amounts of starting material may indicate that the alkoxide ion liberated in the reaction mixture reacts with the product, the alkyne, to regenerate the starting material (scheme 22). The other interesting valid assumption is that it seems that the reaction proceeds with elimination of the hydrogen β to sulfur which is consistent with the fact that only the alkyne thioether and <u>not</u> the alkyne ether was isolated.



84 81



Scheme 22. An attempted synthesis of **81** from **84** and a mechanistic illustration of the possible regeneration of starting material under the reaction conditions.

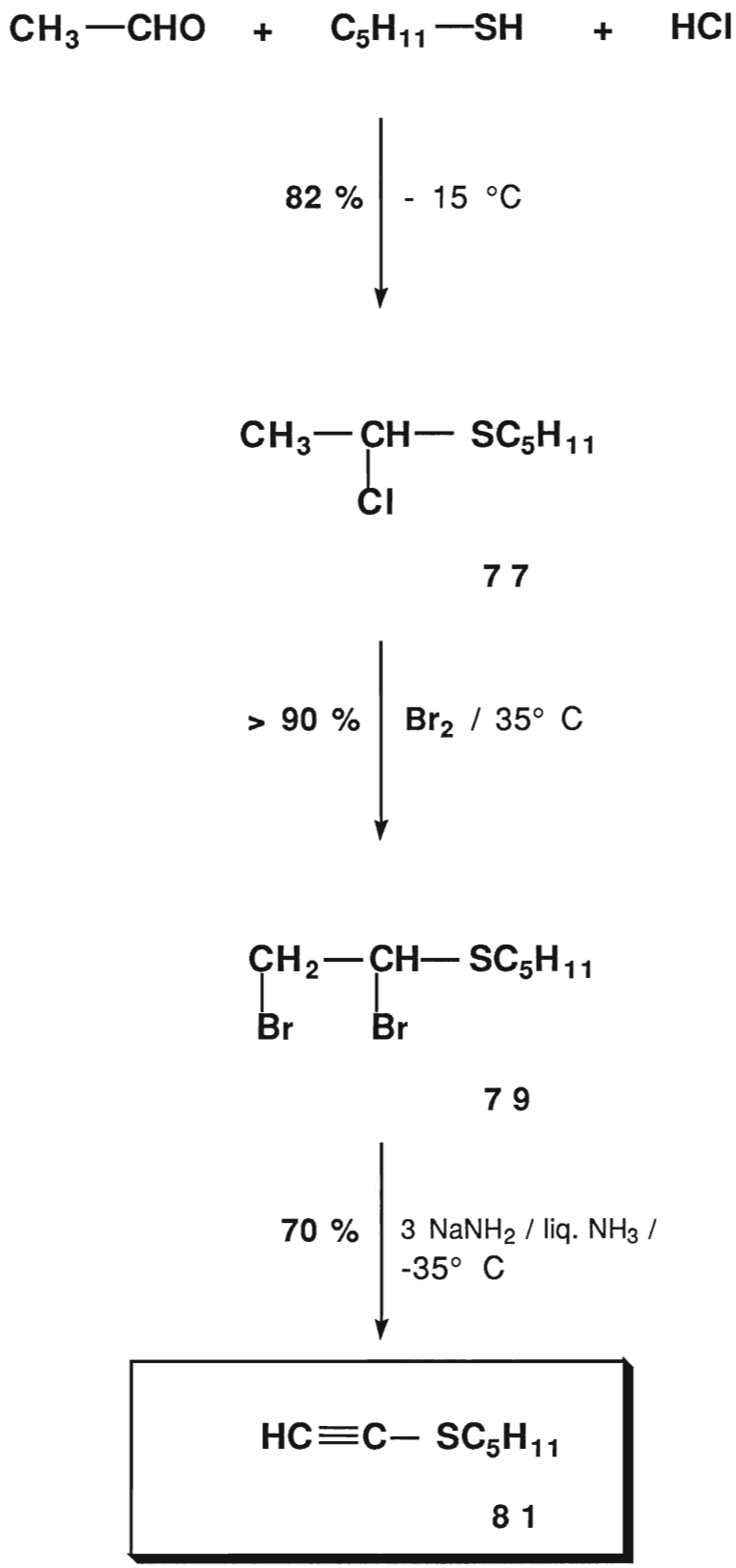
At this stage we were certain that although some of the above methods are to some extent practical, they are for our purposes still unsatisfactory. It seemed beyond doubt that the conditions employed above for the double dehydrobromination of **79** were too aggressive to lead cleanly to the desired alkyne **81**.

In this context, we turned to the alkali metal amides for the double dehydrohalogenation of **79**. Thus, when **79** was added to three equivalents of sodium amide in liquid ammonia, the desired compound **81** was obtained in very good yield. In summary, it appears that this method is the best one among the methods examined for the smooth double dehydrohalogenation of dibromide **79** and the overall reaction sequence illustrated in scheme 23 represents by far the most efficient route to ethynyl n.pentyl sulfide **81**.

II-2. **Preparation of E-2-Iodoethenyl n.pentyl sulfide 85**

In our initial proposal we also required the iodovinyl sulfide **85** to be used as the 15-thia-PGE_1 lower side-chain equivalent. The geometry of the double bond is of course important in that it must be trans which is the geometry present in all natural prostaglandins.

The E-iodovinyl sulfide **85** was conveniently prepared by hydrozirconation[53,63] of the terminal acetylenic sulfide **81** followed by in situ iodination of the intermediate. This conversion proceeds under very mild conditions to give selectively almost 100% of the E-isomer in excellent yield. The stereochemistry of the product was assigned by literature precedent for the formation of E-olefins during reduction of alkynes by these reagents[53,63], and by the observation of a characteristic trans 14.3 Hz coupling between



Scheme 23 . Synthesis of ethynyl n.pentyl sulfide **81** *via* an approach based on elimination reactions.

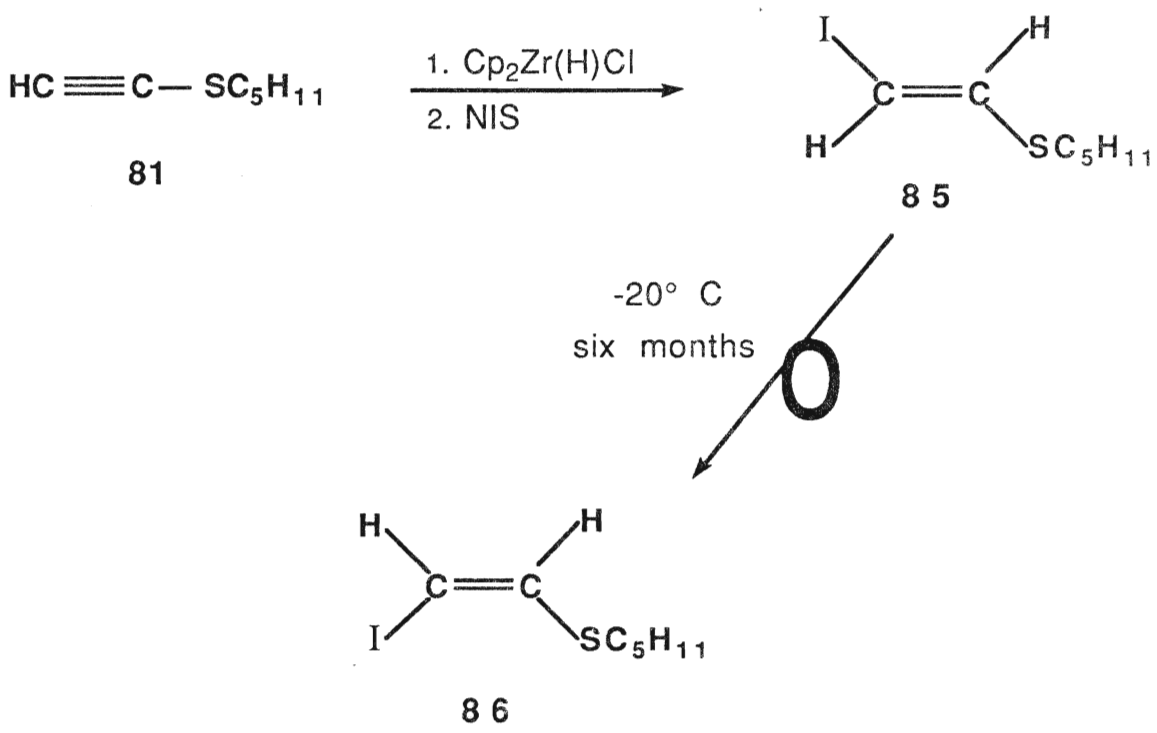
the olefinic hydrogens. Other methods for reductive iodination such as hydroalumination-iodination[64] and hydroboration-iodination[65,66] gave only low yields (20-30%) of the desired product.

The E-isomer of 2-iodoethenyl n.pentylsulfide **85** was found to undergo clean rearrangement to the Z-isomer **86** during storage in solution, even at -20° C. The latter compound is characterized by the 7.1 Hz coupling between its olefinic hydrogens and may be stabilized by a degree of hypervalent bonding[67,68] between sulphur and iodine; analysis via the Alchemy™ modelling software revealed the structure shown in figure **1** with a sulphur-iodine distance of 3.04 A° compared with the sum of the Van der Waal's radii of 3.78 A°.[69] It seems that although, conditions for the rearrangement of E to Z-2-iodoethenyl alkyl sufides have not been investigated, the latter compounds are also accessible by this route.

III- **Preparations of simple cyclopentenone derivatives and model conjugate addition reactions.**

III-1. **Preparation of cyclopentenone derivatives.**

Because we desired to test the feasibility of our initial proposal, we required simple cyclopentenone derivatives to be used for the conjugate addition reaction. In view of this, we obtained 2-cyclopentenone, 4-(tetrahydropyran-2-yloxy)-2-cyclopentenone **52**, and 4-(triethylsilyloxy)-2-cyclopentenone **53**. 2-Cyclopentenone was purchased from Aldrich and the other two cyclopentenone derivatives were synthesized.



Scheme 24. Preparation of (E)-iodovinyl n.pentyl sulfide **85** and its rearrangment to the (Z)-isomer **86**

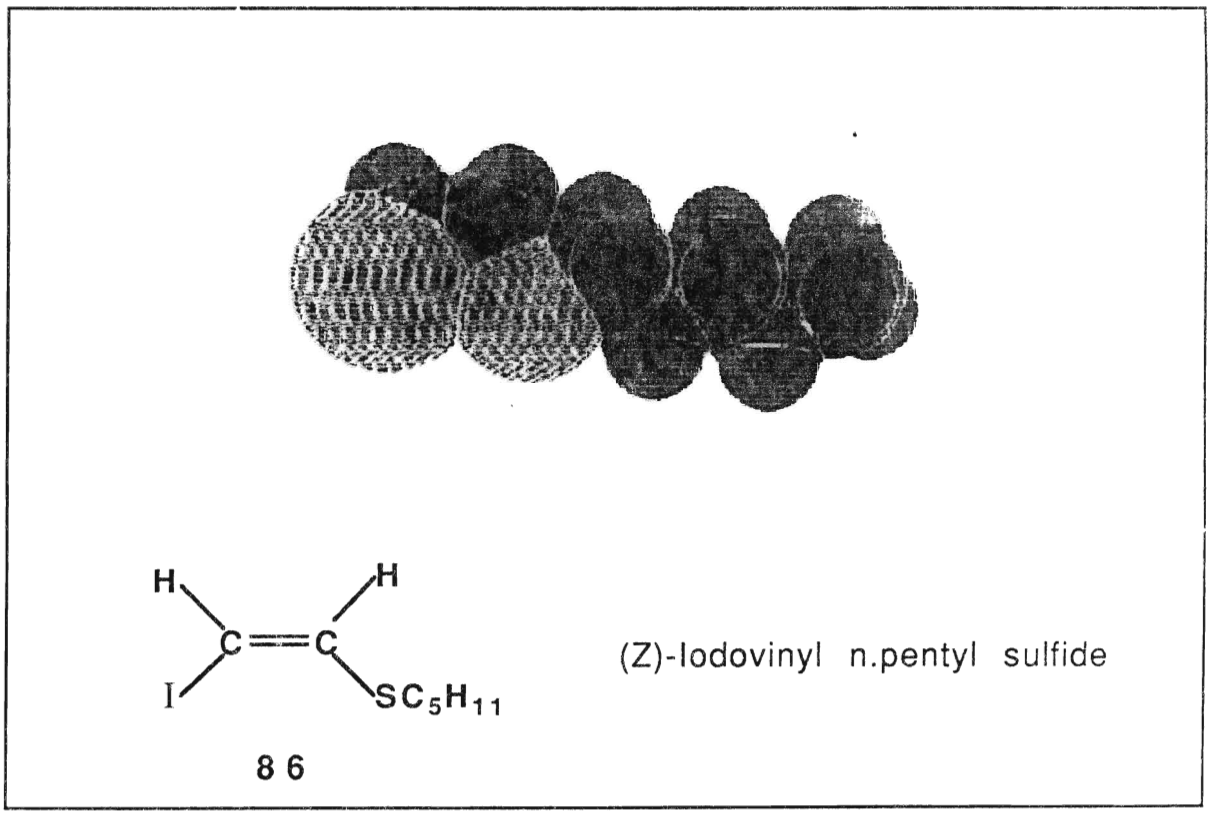


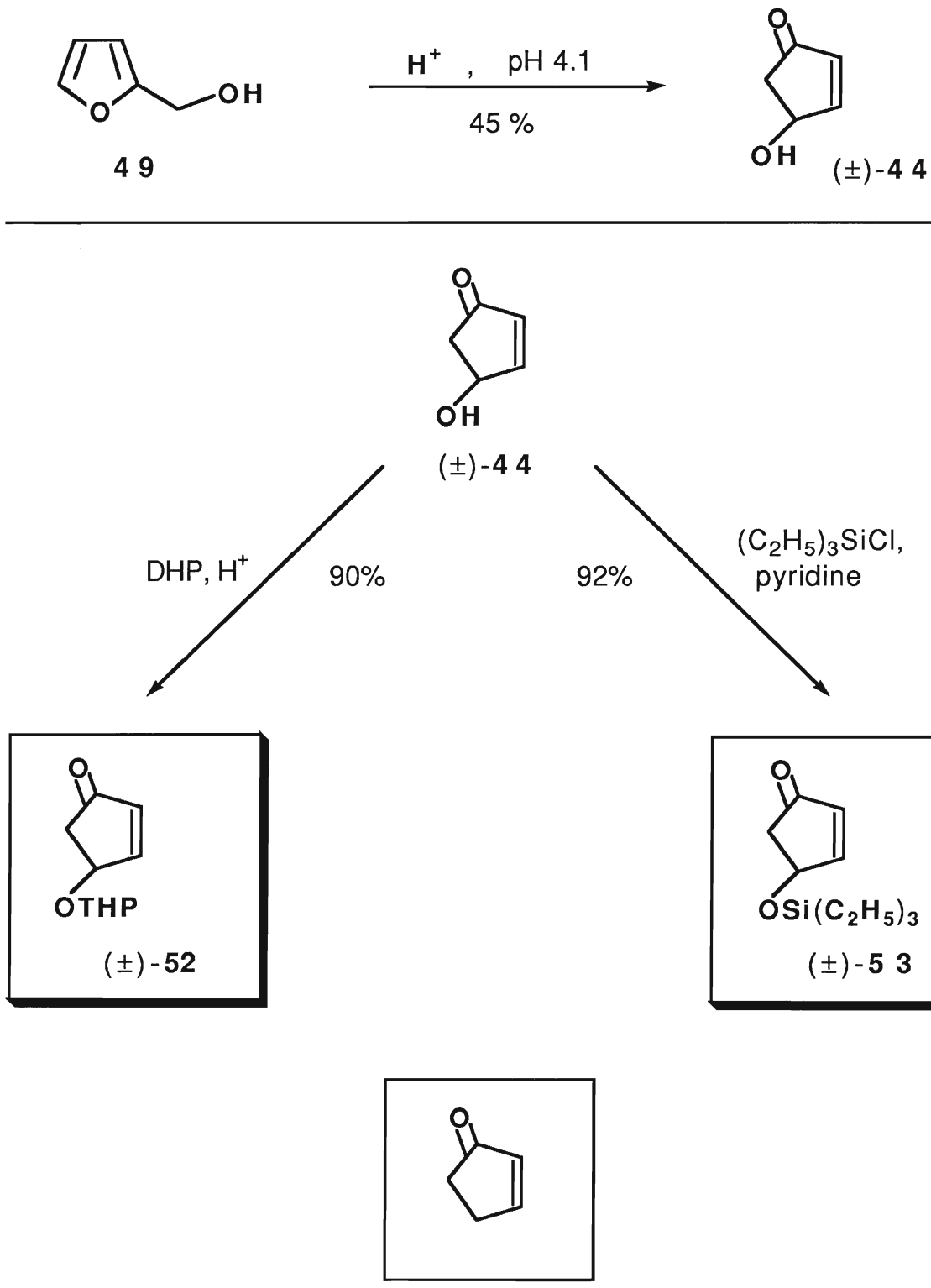
Figure 1. A model of **86** revealed by the Alchemy™ modelling software

The synthesis of the 4-substituted cyclopentenone derivatives **52** and **53** involved the preparation of the common intermediate 4-hydroxy-2-cyclopentenone **44**. Compound **44** was prepared by an acid catalysed rearrangement of 2-furfuryl alcohol **49**.[37] This remarkable rearrangement which proceeds with good yield probably involves initial opening of the furan ring giving an intermediate which undergoes an intramolecular cyclization producing the hydroxy enone.

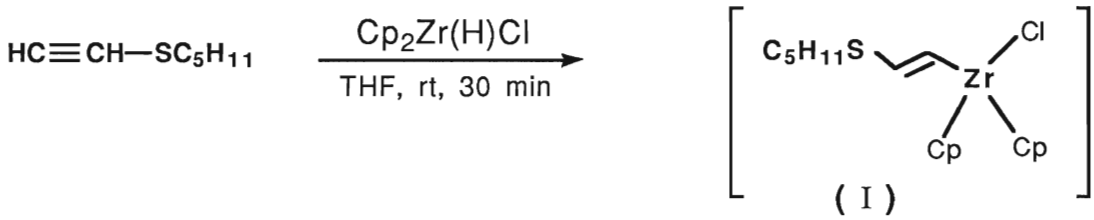
III-2. **Model conjugate addition reactions.**

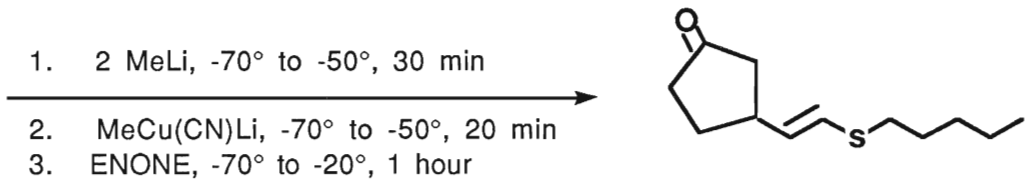
Before going into the trouble of synthesizing the final target synthon **37** (or its silyl derivative **38**) which carries the upper side-chain and the 4-protected hydroxy substituent, we wanted to investigate the feasibility of the conjugate addition reaction using the readily accessible cyclopentenone derivatives mentioned above. Therefore, we first tried this method using 2-cyclopentenone. The idea was that if the addition works with this model compound, it should as well work with the substituted enone derivatives.

When we carried out the conjugate addition[53] according to scheme 26, we were pleased to discover that the addition proceeded in good yield to afford compound **87**. More importantly, the integrity of the double bond (trans) was preserved as confirmed by NMR analysis. Next, we desired to see if the conjugate addition is actually stereospecific. In view of this, we carried out the conjugate addition process using 4-(triethyl silyloxy)-2-cyclopentenone **53** as the enone. After flash column chromatography on the crude product we isolated compound **89** in 55% yield (Table **3**, entry 3).



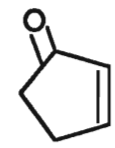
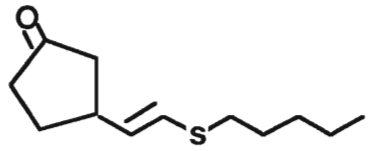
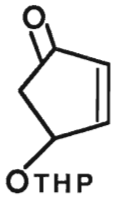
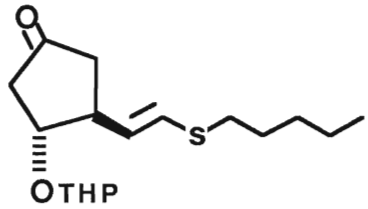
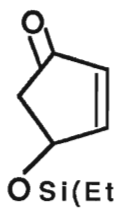
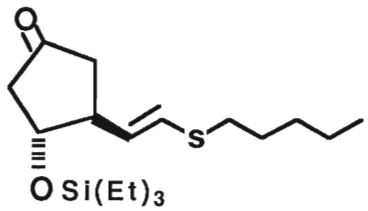
Scheme 25. Synthesis of 4-hydroxy-2-cyclopentenone (±)-**44** and its tetrahydropyranyloxy and triethylsiloxy derivatives.





(eq. 6)

Table 3. 1,4-Addition reactions of mixed vinylic cyanocuprates with simple enone systems.

entry	enone	acetylene	product	% yield
1		HC≡CH—SC5H11	 **87**	70[a]
2	 OTHP (±)-**52**	HC≡CH—SC5H11	 OTHP (±)-**88**	58[b]
3	 OSi(Et)3 (±)-**53**	HC≡CH—SC5H11	 OSi(Et)3 (±)-**89**	55[a]

a. chromatographically isolated material.

b. crude product.

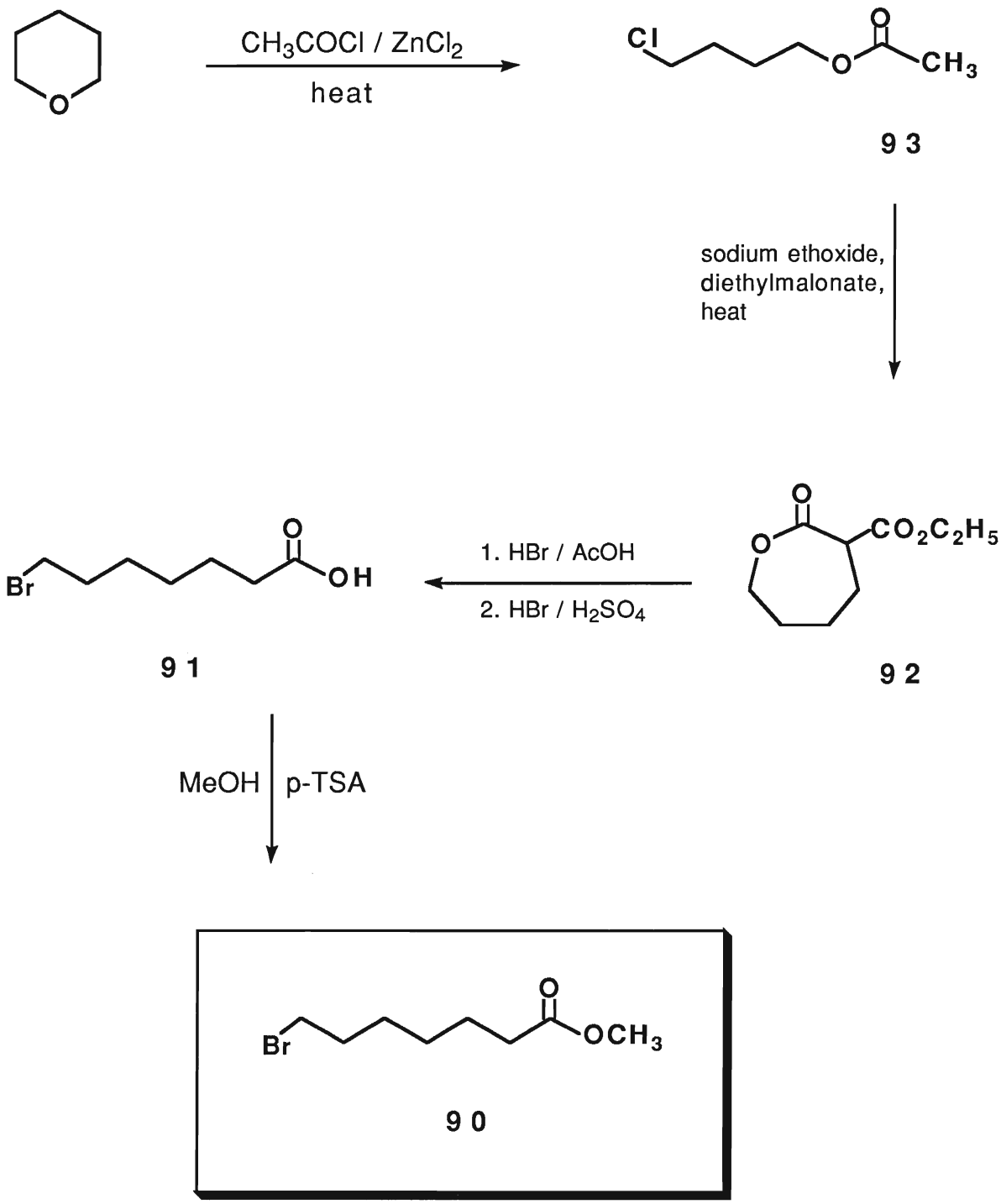
The 3,4-trans relationship on the ring was assigned on the basis of literature[53,63] precedent which reveals the regio-specificity of this type of conjugate addition method. ^{13}C NMR analysis showed a single set of signals assignable to 14 carbons in this structure indicating a single isomer. At this stage, and after we sorted out the two main concerns, the feasibility and the efficiency of the method, we were quite comfortable with proceeding to the synthesis of the target synthon **37** required for the total synthesis of the desired 15-thia PGE_1 analog .

IV- Preparation of the cyclopentenone nucleus carrying the upper side chain and synthesis of 15-thia PGE_1.

IV-1. Preparation of the upper side-chain equivalent.

Methyl 7-bromoheptanoate **90**[19] which represents the upper side chain equivalent of the prostaglandin skeleton and which is to be installed on the cyclopentenone ring, was synthesized as outlined in scheme 26. Thus, tetrahydropyran was converted to 5-chloroamyl acetate **93** by acetyl chloride in the presence of zinc chloride. Zinc chloride seems to play a catalytic role and without it only starting material was recovered. It was also shown that the use of freshly redistilled starting material improved the yield of the reaction considerably.

The chloroester was then treated with a refluxing solution of sodiomalonic ester in ethanol to give lactone **92**. The lactone was subsequently decarboxylated using a mixture of hydrobromic-acetic acids and then hydrolysed and brominated using another mixture of hydrobromic-sulfuric acids to give 7-bromoheptanoic acid **91**.



Scheme 26. Preparation of the upper side-chain equivalent : Methyl 7-bromoheptanoate **90**.

Esterification of the organic acid in the usual way then furnished the required bromoester **90**.

IV-2. **Instalment of the upper side chain onto the cyclopentenone nucleus.**

The chiral building block **1** was prepared in racemic form by a step-wise synthesis as illustrated in scheme 27. The synthesis resembles the Bagli's route (scheme 7) but with some important modifications.

The standard method[70] for the alkylation of the potassium enolate **94** of ethyl 2-oxocyclopentane carboxylate **20** was found to be not very efficient. This might be due to the fact that the insolubility of **94** in toluene, which led to caking, could have resulted in thermal decomposition. Furthermore, we encountered some difficulties in obtaining a completely anhydrous preparation of potassium enolate **94**. On the other hand, the sodium enolate **95**, prepared *in situ* with sodium hydride[15], was soluble in hot dimethoxyethane and its alkylation with bromo ester **90** proved more convenient.

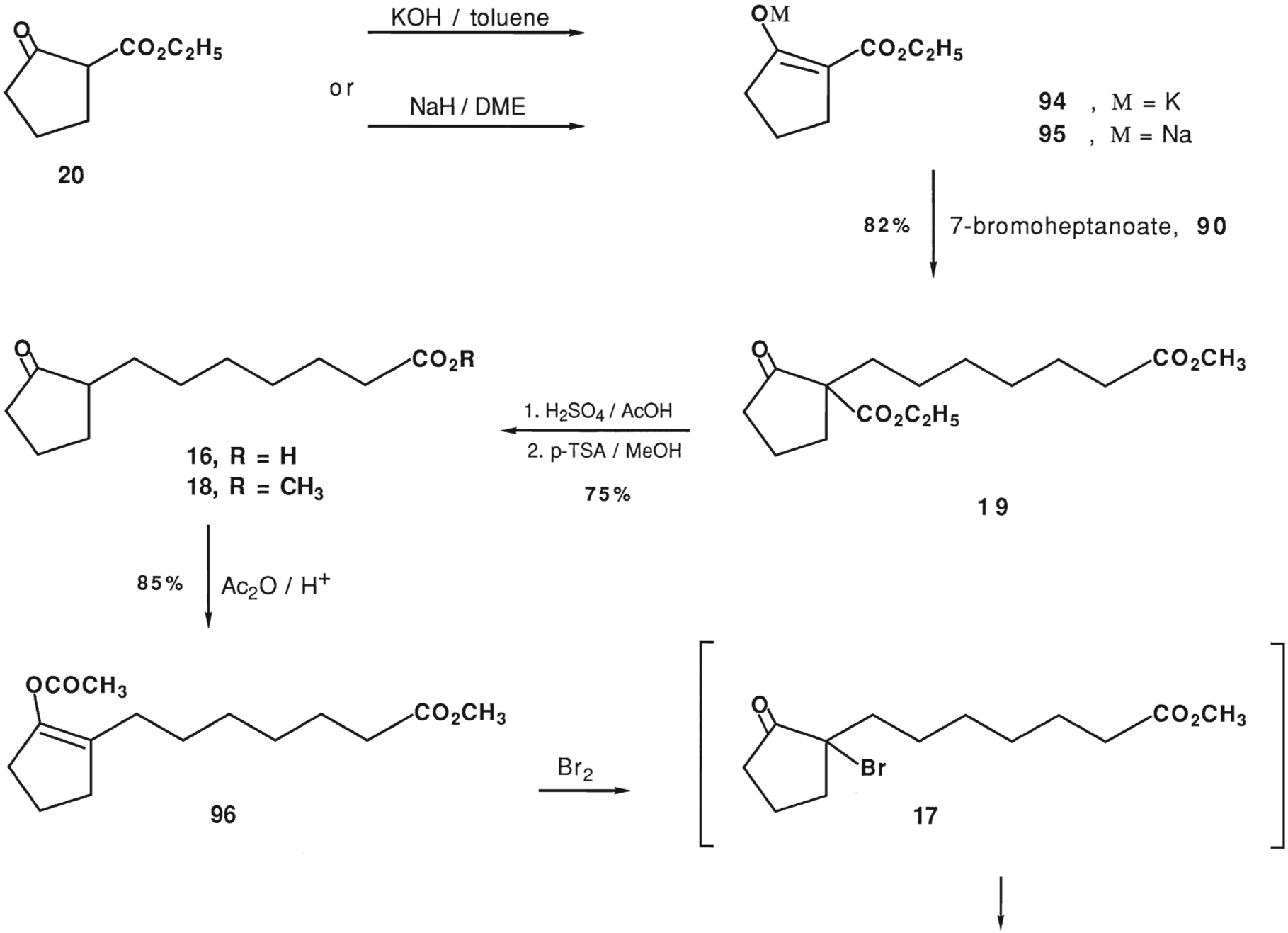
Therefore, treatment of **95** with methyl 7-bromoheptanoate **90** provided the expected alkylation product **19** in 82% yield. Decarboxylation was then carried out by refluxing the keto diester **19** in a mixture of aqueous sulphuric acid and acetic acid. Simple mineral acid decarboxylation[14] was very slow. The crude keto acid **16** was esterified in the standard way by refluxing with methanol and benzene in the presence of p-toluenesulfonic acid using a Dean-Stark separator. If the amount of the keto acid **16** to be esterified is

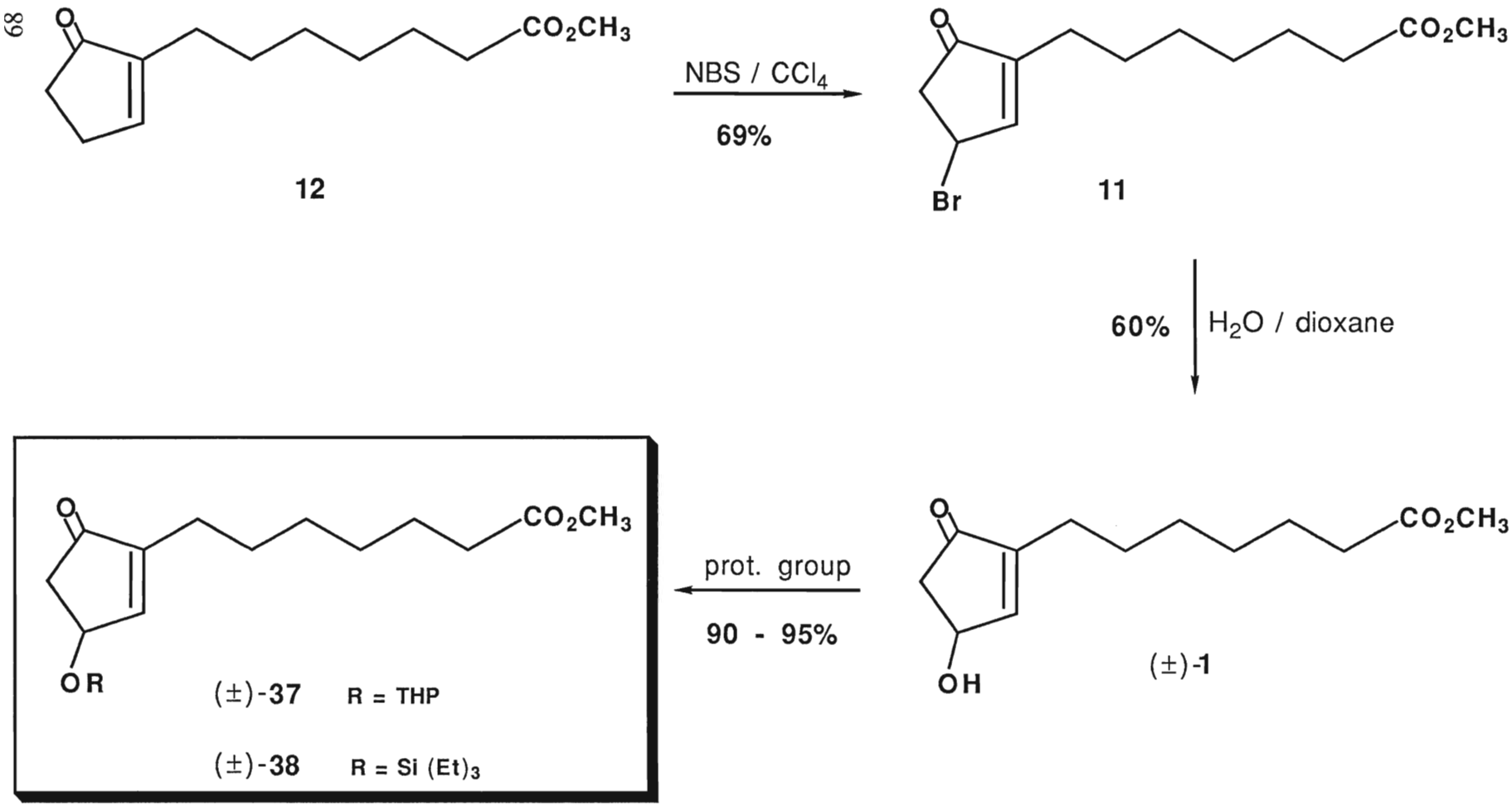
small, we recommend that the esterification should be carried out using diazomethane since this method proved more convenient and produced a higher yield than the former method. Another alternate decarboxylation route may be carried out by refluxing the keto diester **19** with sulphuric acid in methanol. Although we did not test this idea, it seems feasible and if it works it could eliminate the re-esterification step.

The conversion of cyclopentanone **18** to cyclopentenone **12** was accomplished by a bromination-dehydrobromination method.[15] Treatment of cyclopentanone **18** with acetic anhydride in the presence of p-toluene sulfonic acid led to the enol acetate **96** which was brominated achieving a regioselective halogenation. Direct bromination of **18** was not a clean reaction, leading to a mixture of monohalogenated and polyhalogenated ketones.

The crude 2-bromo ketone **17** was then dehydrobrominated without delay. Thus, bromo ketone **17** was added to a refluxing anhydrous mixture of lithium bromide and lithium carbonate in dimethyl formamide. The crude product was then purified by distillation to give pure cyclopentenone **12**. It should be mentioned that all the above cyclopentanone derivatives (with the exception of the bromo ketone **17** which was not purified) are high boiling oils and their purification by distillation must be carried out at very low pressure otherwise charring and decomposition of these compounds will take place.

There are various ways (see introduction) of introducing the hydroxyl group into the 4-position of cyclopentenone **12**. For convenience and availability of chemicals we choose the most recent


KOH / toluene
or
NaH / DME
20
94 , M = K
95 , M = Na
82%
7-bromoheptanoate, 90
19
1. H2SO4 / AcOH
2. p-TSA / MeOH
75%
16, R = H
18, R = CH3
85%
Ac2O / H+
96
Br2
17



Scheme 27. Synthesis of 4-substituted 2-cyclopentenone derivatives : **37** and **38**.

method[11] which involved the standard allylic bromination of cyclopentenone **12** followed by hydroxylation of the known 4-bromo ketone **11** using water in refluxing dioxane (see scheme 27). Once the 4-hydroxycyclopentenone **1** was obtained, we had to protect it so we could use it in the conjugate addition step. We needed a protecting group which is removable by mild acidic conditions to which the ß-ketol system would be stable. All of these requirements were satisfied by both the tetrahydropyranyl and the triethylsilyloxy protecting groups.

IV-3. **Developing a synthesis of the protected 15-thia-PGE_1 97.**

With the required building block **37** in hand, we then carried out the synthesis of the methyl ester 15-thia-PGE_1 by the previously mentioned 1,4-addition method. When we conducted the addition under the same conditions mentioned above, we were disappointed to find out that none of the addition product was formed and only the starting enone was recovered. We repeated the experiment taking extra care but without success.

At this point we did not have an explanation other than the suspected bad quality of the reagents, in particular the Schwartz's reagent, $Cp_2Zr(H)Cl$. To test the quality of this reagent, the presumably formed E-vinylzirconate intermediate (I) (eq. 6) was trapped in situ with N-iodosuccinimide. This resulted in the formation of the expected E-iodovinyl sulfide in excellent yield and selectivity which indicated that the Schwartz's reagent was indeed in good condition.

Next, we considered the conjugate addition step itself, that is, the addition of the enone. We thought probably the reaction temperature was too low to allow for overcoming the activation energy barrier for the reaction. In this respect, we carried out the conjugate addition step by adding the enone at -70° C and allowing the reaction mixture to warm up to -20°C and keeping it at that temperature for 1 hr before quenching with the NH_4Cl/NH_4OH solution. After work up and analysis of the crude product, we found out that a 1,4-addition adduct was formed in good yield. However, ^{13}C NMR analysis of the chromatographed deprotected product showed multiple sets of signals indicating a mixture of at least 4 compounds even though the material shows as only one spot on TLC.

A possible explanation of this is that an isomerization at C-8 might have occurred at that particular reaction temperature, thereby making the conjugate addition non-stereospecific. At this point we realized that low reaction temperature (below -50°C) is essential for the conjugate addition to be stereospecific.

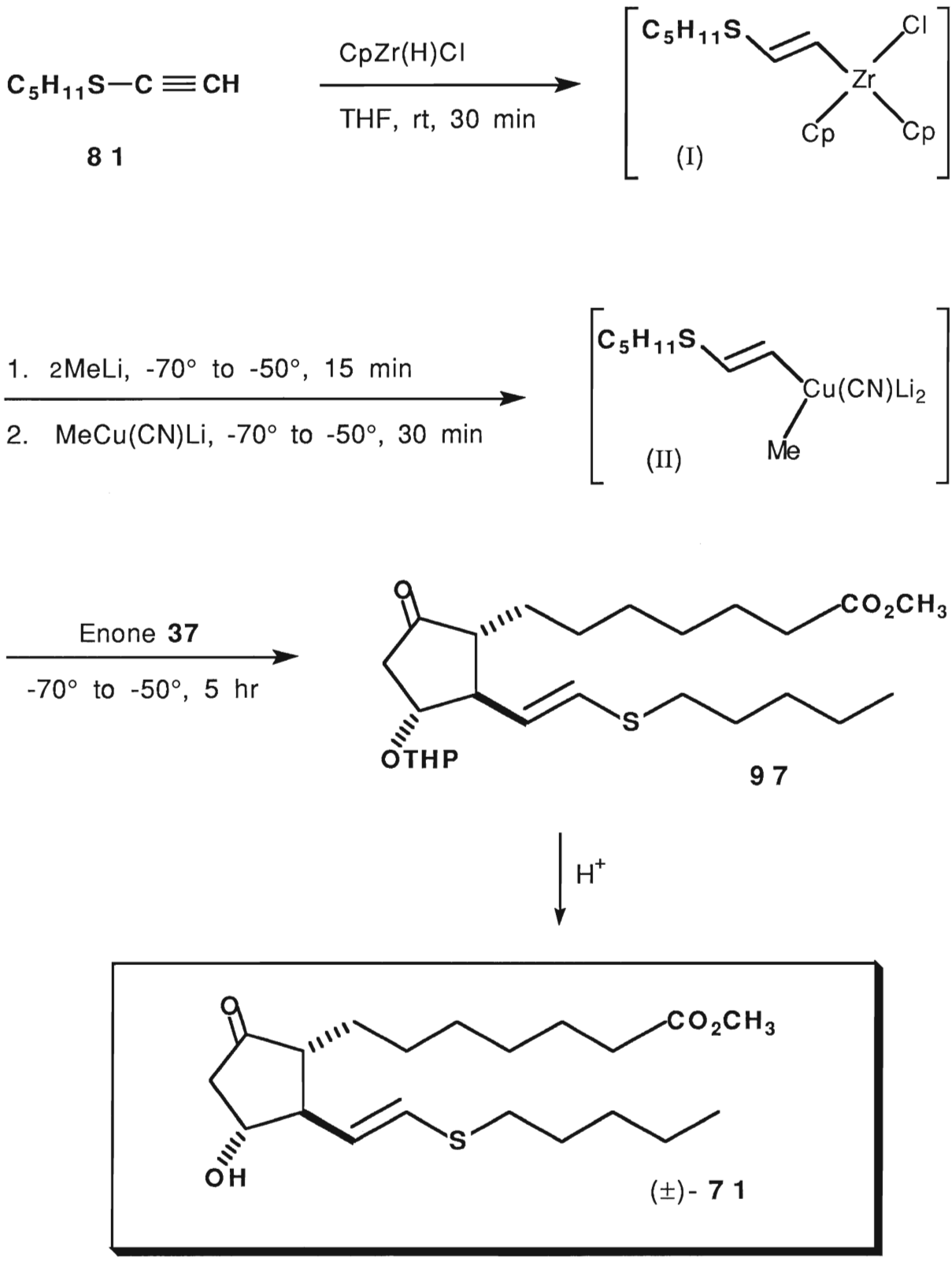
IV-4. **Synthesis and purification of 15-thia-PGE$_1$ 71.**

Therefore, we repeated the experiment as in scheme 28 as follow : hydrozirconation of the acetylenic sulfide **81** with $Cp_2Zr(H)Cl$ in the usual way gave the alkenylzirconium intermediate (I). Transmetalation of the alkenylzirconium intermediate (I) was then accomplished by adding 2.0 equivalents of methylithium at -70° C and the mixture warmed up to -50° C for 15 min, and recooled to -70° C. The subsequent addition of a cooled solution (-70°) of

MeCu(CN)Li (from MeLi + CuCN in THF) presumably results in the situ generation of the mixed high order cyanocuprate intermediate (II). Treatment of (II) with enone **37** at low temperature (-70° to -50°) for 5 hours then gave the protected 15-thia-PGE_1 analog **97**.

The crude product was cleaned by flash chromatography to give the pure THP derivative **97** of the 15-thia PGE_1 analog **71** as a pair of diastereoisomers as judged by ^{13}C NMR and HPLC analyses. Deprotection of **97** then gave the desired 15-thia-PGE_1 analog **71** (scheme 28) which was purified by column chromatography and preparative HPLC. ^{13}C NMR (figure 4) and HPLC analysis indicated that the compound was a single isomer, that is, a pair of enantiomers.

At this stage, it is important to mention that the conjugate addition reaction presented above must be conducted in the stated way in order to insure its maximum efficiency (see also above). For example, it was very interesting to find out that when the reaction was conducted by adding the cyanocuprate $Me_2Cu(CN)Li_2$ (separately made from CuCN and 2 molar equivalents of methyllithium in ether at -70° to -10°) at - 70° C to the vinylzirconium intermediate (I), previously treated with one molar equivalent of methyllithium, and subsequent addition of the enone, the major product was the 3-methyl cyclopentanone derivative **98**.



Scheme 28. Synthesis of methylester 15-thia-PGE_1 analog **71** *via* in situ cuprate formation / conjugate addition reaction.

Figure 2. HPLC chromatograph of the target molecule, 15-thia-PGE_1. The chromatograph to the right-hand side is an injection of sample (50 μL) during purification by preparative HPLC.

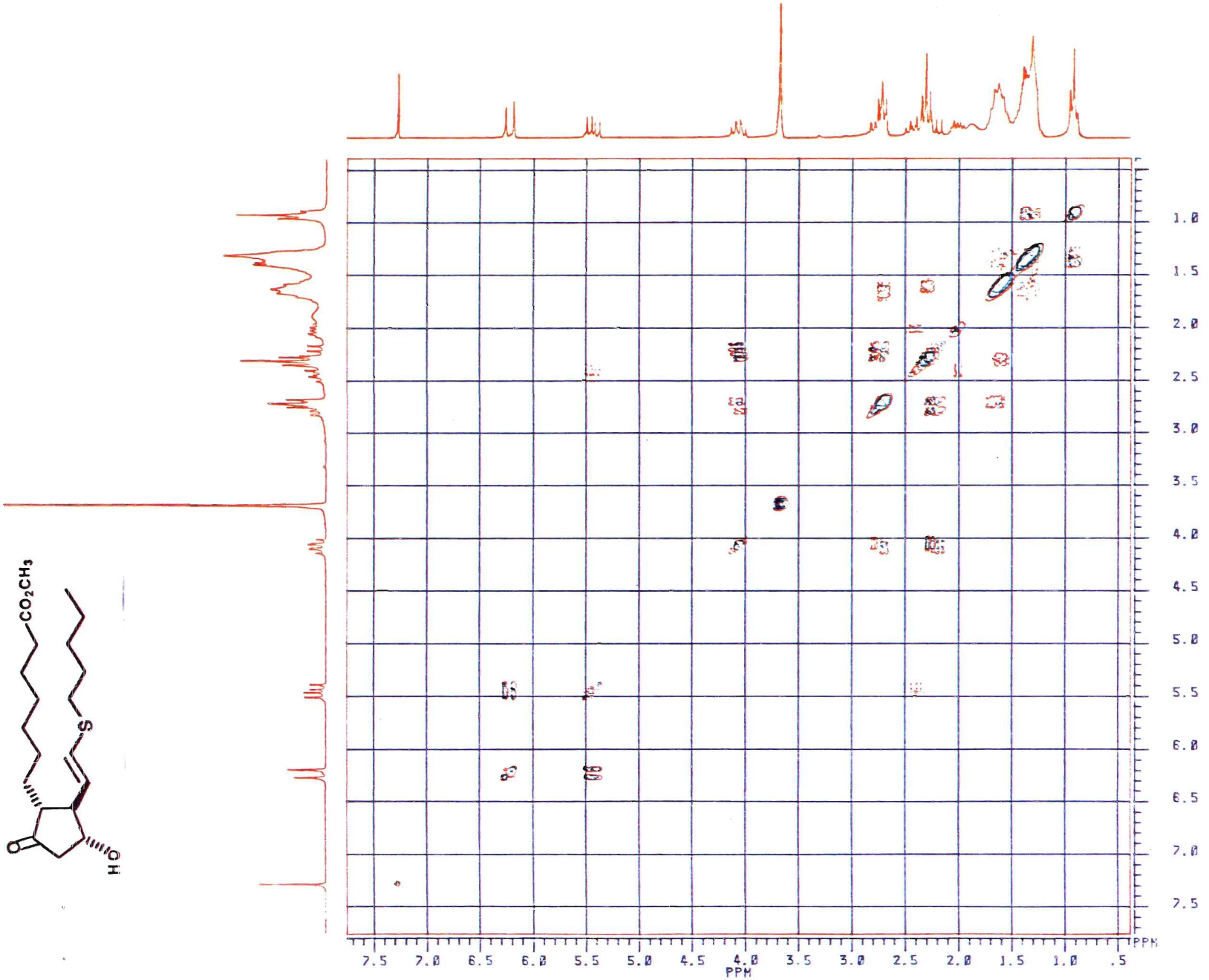
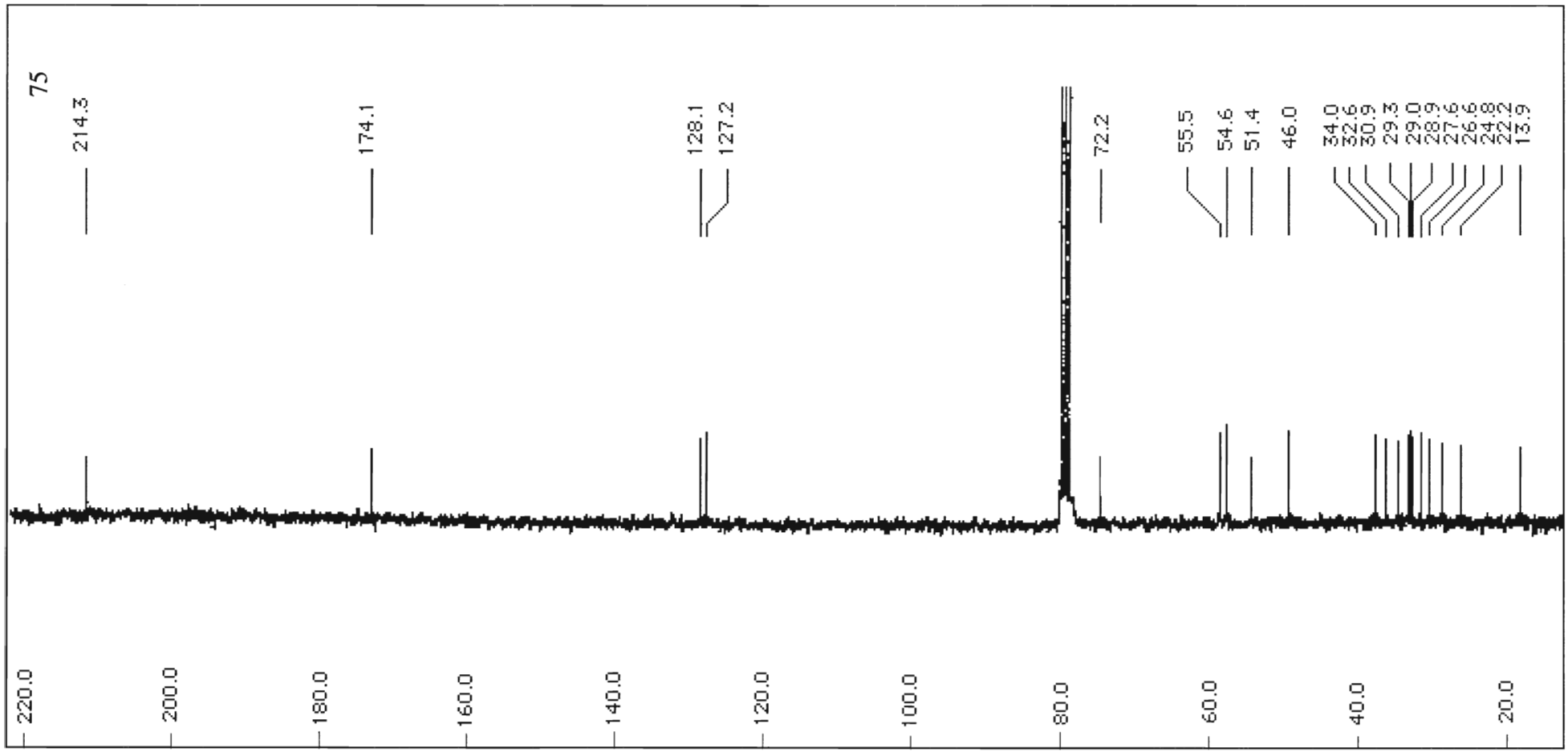
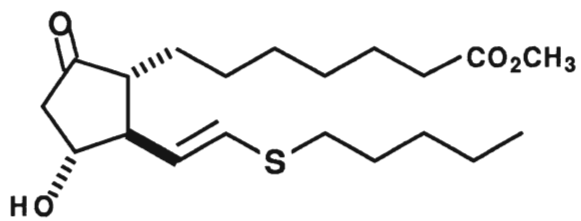


Figure 3. 2D ^{1}H NMR spectrum of 15-thia-PGE_1 methyl ester, analog **71**.





Target compound **71**

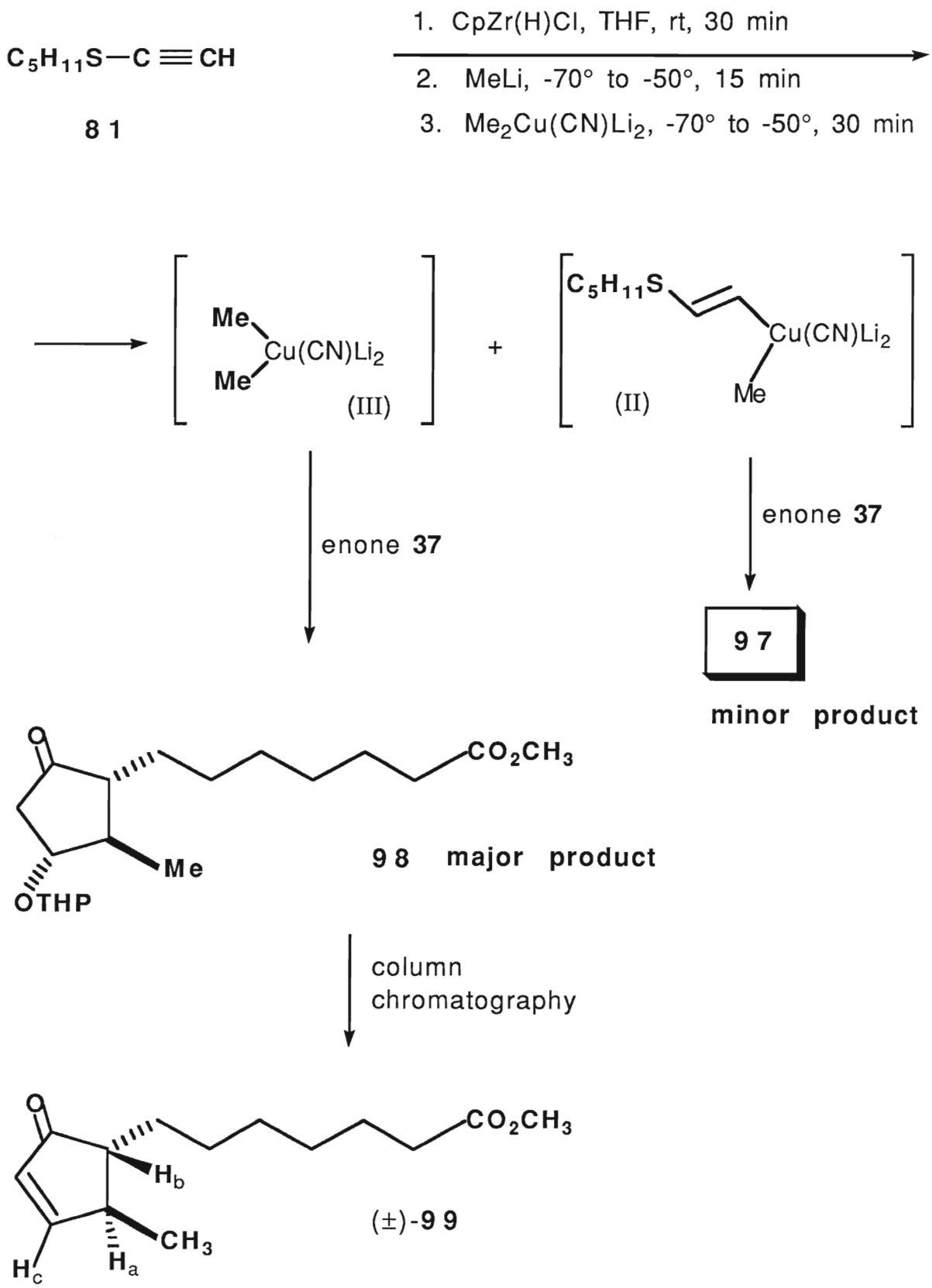
Figure 4. ^{13}C NMR spectrum (200 MHz) of 15-thia-PGE_1 methyl ester, analog **71**.

The formation of this unexpected product which was obtained favourably (8 : 2) over the usual conjugate addition adduct **97** may be rationalized in the following context.

There may have been some ligand transfer selectivity in favour of the methyl group when the enone was added to the presumably mixed high order cyanocuprate intermediate (II). However, based on our results of the previously discussed conjugate addition reactions and also on literature precedence this would be very unlikely. In all the other conjugate addition reactions we never detected any amounts of such an adduct.

The other likely route to **98** is from the reaction of the high order cyanocuprate $Me_2Cu(CN)Li_2$, intermediate (III), with enone **37** (scheme 29). This indicates that the intermediate (II) necessary for the vinyl ligand transfer was not made in appreciative amounts which in turn suggests that the expected Zr-to-Cu transmetalation was not effected efficiently. This also explains why the expected conjugate addition adduct **97** was obtained only in small amounts.

The assignment of the trans relationship of the substituents on the ring in (±)-**99** was based on coupling constants with respect to approximated dihedral angles predicted by the Karplus equation. Thus after identifing the ^1H NMR signal for $\mathbf{H}_a$ in (±)-**99**, with the help of 2D NMR experiment, which appeared as a complex multiplet, we did a decoupling experiment in which we irradiated at the methyl group and allowed $\mathbf{H}_a$ to couple with only $\mathbf{H}_b$ and $\mathbf{H}_c$. This simplified the complex multiplet to a double doublet with J values of 2 Hz and 7 Hz which suggested trans relationship as predicted by the Karplus curve for cyclopentane derivatives.



Scheme 29. A possible route to **98** during cuprate conjugate addition.

CONCLUSIONS:

This study revealed a convenient synthetic approach for the preparation of the desired ethynyl n.pentyl sulfide **81**. This approach (see scheme 23) which could be used for the synthesis of other long chain ethynyl sulfides is convenient and gives high yields of pure products. Furthermore, the valuable isomerically pure E-iodovinyl sulfide **85** was prepared in excellent yield by a hydrozirconation-iodination approach of **81**. This general protocol provides a short synthetic route to isomerically pure halovinyl sulfides which were hitherto difficult to make.

The method employed for effecting the 1,4-conjugate addition method involved the in situ generation of high order cyanocuprate reagents. In addition to eliminating the need for isolating the unstable iodovinyl sulfide, the method proved to be convenient and stereospecific.

The newly made 15-thia-PGE_1 analog is interesting in that it possesses a different, yet closely related, functionality in the position (C-15) where the initial biochemical reaction takes place in natural PGE_1. The biological behaviour of this analog is under investigation.

EXPERIMENTAL

I– GENERAL.

A) Spectrometers:

IR spectra were obtained with an Analect FX 6260 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC200 or on a Bruker AM 500 spectrometer. Chemical shifts of ^{1}H NMR are reported in δ values relative to tetramethylsilane (δ 0) or chloroform-d (δ 7.27). Splitting patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qu, quintet; m, multiplet and b means a broad signal. Mass spectra (MS) were recorded on Kratos concept IS double focusing mass spectrometer with combined EI / CI and FAB sources.

B) Chromatography:

i-Thin Layer Chromatography. R_f values on TLC were recorded on E. Merck precoated (0.22 mm) Silica Gel 60 F_{254} plate. The plates were sprayed with a solution of 2O% ethanolic sulfuric acid and then heated until the spots became clearly visible.

ii-Column Chromatography. Normal and flash column chromatography were conducted on silica gel from Terochem Laboratories Ltd. (equivalent to Merk 7734).

iii-High Performance Liquid Chromatography. The high-performance liquid chromatography (HPLC) for analysis of purity and the preparative HPLC were carried out on a Perkin Elmer Model with Series 3 Liquid Chromatograph : column ODS2C-18; solvent, chloroform; pressure, 5-6 Kg / cm^2; flow rate, 1.5 mL / min; detection, UV (254 nm).

C) Solvents:

Ether, tetrahydrofuran (THF) and benzene were dried by distillation over Na-benzophenone ketyl under argon atmosphere. Dry dichloromethane (CH_2Cl_2), and carbon tetrachloride (CCl_4) were obtained by distillation over P_4O_{10}. Dry N,N-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were prepared by distillation from CaH. Solutions obtained after work-up and extraction were routinely dried over anhydrous sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) and evaporated by a rotary evaporator under aspirator pressure.

D) Reagents and materials:

Commercial n-butyllithium in hexane solution (Aldrich), methyllithium in ether solution (Aldrich), and t-butyllithium in pentane solution (Aldrich) were used directly from the bottle.

II- Preparation of the lower side-chain equivalents.

II-1. Attempted one stage approaches of preparing ethynyl n.pentyl sulfide 81.

An addition-elimination approach .

To a vigorously stirred suspension of 3.74 g (0.0960 mol) of sodium amide in liquid ammonia (50 ml), 4.65 g (0.0480 mol) of cis-1,2-dichloroethene was cautiously added (exothermic reaction) over 5 minutes. After 0.5 hr, 5.00 g (0.0480 mol) of n.pentylthiol was added and the reaction mixture was stirred for another 0.5 hr at the boiling point of liquid ammonia. The ammonia was allowed to

evaporate (under dry conditions) overnight and the mixture was then worked-up by the addition of ether and water. After separation, the aqueous layer was extracted once with ether and the combined etheral extract was dried ($MgSO_4$) and evaporated. The residue was distilled on Kugelrohr. The fraction collected at 60-70° C / 0.7 torr was characterized to be cis-2-chloroethenyl-1-n.pentyl sulfide **74** (10%).

The title compound showed the following spectral data : ^1H NMR : δ = 0.91 (t, 3H, CH_3-), 1.34-1.43 (m, 4H, CH_3-(CH_2)$_2$-), 1.59-1.69 (m, 2H, -CH_2-CH_2-S), 2.71(t, 2H, -CH_2-S), 6.04 and 6.32 (each d, 1H, J = 6 Hz , =CH); ^{13}C NMR : δ = 13.8 (CH_3), 22.2, 30.1, 30.6 (CH_2's), 33.5 (CH_2-S), 113.9 and 129.1 (olefinic carbons); MS (EI), m/z (%) : 164 (M^+, 13), 129 (M^+ - 35, 5), 94 (12), 71 (27), 55 (26), 43 (15).

The undistilled material was found to be cis-bis-(1,2-n.pentylthio) ethylene **73**; TLC, R_f = 0.70 (1 : 1 / ethyl acetate : hexane). ^1H NMR indicated the same types of signals for the pentyl chain as those reported above and a doublet (J = 6.5 Hz) at 6.05 for the vinylic protons HC=CH); ^{13}C NMR : δ = 13.66 (CH_3), 22.0, 29.8, 30.5 (CH_2's), 34.1 (CH_2-S), 123.3 (CH=CH); MS (EI), m/z (%) : 232 (M^+, 100), 162 (72), 129 (14), 92 (88), 71 (29), 55 (26), 43 (91).

A thiolation-alkylation approach .

A 250-ml three-necked round-bottomed flask equipped with a mechanical stirrer, an ammonia condenser, and a thermometer was flushed with argon and charged with 3.68 g (40.0 mmol) of the lithium acetylenide-ethylenediamine complex. After the flask was

cooled below the boiling point of liquid ammonia, 50 ml of ammonia was condensed. After stirring the mixture for five minutes at -35° C , the ammonia condenser was removed and finely powdered and dried sulphur (40.0 mmol) was added quickly in small portions. The element dissolved instantaneously to form an orange-brown solution. The mixture was then stirred at - 35° C for 15 minutes and 9.90 g (50.0 mmol) of n.pentyl iodide (or bromide) was then added via a glass syringe over 2 minutes. When the addition of the alkyl halide was complete, the mixture was stirred at the boiling point of liquid ammonia for 4 hours. Stirring was then stopped and the ammonia was allowed to evaporate overnight. The remaining residue was worked up by the addition of water and ether. The ether layer and three ether extracts of the aqueous layer were combined and dried. After distilling off the solvent, the remaining brown oil was distilled in vacuo to afford 25% of pure ethynyl n.pentyl sulfide as identified by NMR and IR analysis.

In an attempt to develop a method for the synthesis of **81** using this thiolation alkylation sequence, different reaction conditions were used (see table **1**) but without very much success.

II-2. **Multi-step approaches for the synthesis of ethynyl n.pentyl sulfide 81.**

1-Chloroethyl n.pentyl sulfide 77.

In a 1-liter round-bottomed 4-necked flask, provided with a gas inlet and a gas outlet tube, a mechanical stirrer, and a thermometer, were placed 44.1 g (1.00 mol) of acetaldhyde and 20 g of n.pentylthiol. The mixture was cooled at -20° C (dry ice +

acetone) and a vigorous stream of hydrogen chloride was introduced below the surface of the liquid mixture to the point of saturation. The remainder of the required 1.00 mol of pentylthiol was then added drop-wise, maintaining the temperature at -10° C (occasional interruption of the introduction of hydrogen chloride or the thiol may be necessary). The HCl is allowed to bubble in the reaction mixture until thick clouds (of hydrogen chloride) escaped from the outlet tube to the bubbler. Stirring was continued at -10° C for another 15 minutes and then at room temperature for 20 minutes to remove excess hydrogen chloride. Pentane (50 ml) was then added to the reaction mixture. After 10 minutes the upper layer was separated off and the aqueous layer was extracted four times with 50-ml portions of pentane. The extracts were then dried ($MgSO_4$) and pentane removed (rotary evaporator). The residue was quickly distilled in vacuo through a 25 - cm Vigreux column, the receiver being cooled at -10° C. Care should be taken that the temperature of the bath is not too high otherwise elimination of hydrogen chloride to form the unsaturated thioether takes place.

The colourless liquid (80%, very distinctive smell) collected at 39° C / 0.3 torr was used for further conversions. The residue was mainly dipentyl thioacetal. The α-chlorothioether was stable for several months at - 5° C ; TLC, R_f = 0.71 (1 : 1 / ethyl acetate : hexane).

The structure of the compound was evident by its spectral data : ^1H NMR : δ = 0.92 (t, 3H, C**H**$_3$-), 1.26 - 1.41 (m, 4H, CH_3-(C**H**$_2$)$_2$-), 1.56-1.68 (m, 2H, -C**H**$_2$-CH_2-S-), 1.85 (d, 3H, C**H**$_3$-CHCl-), 2.62-2.88 (m, 2H, -S-CH_2-), 5.26 (q, 1H, -S-C**H**Cl); ^{13}C NMR : δ = 13.6 (CH_3-),

26.3 (**C**H_3-CCl), 22.1, 20.4, 30.9, (3 CH_2's), 31.9 (**C**H_2-S), 64.2 (**C**-Cl); MS (EI), m/z (%) : 131 (M^+ - Cl, 100), 115 (2) 103 (4), 75 (42), 69 (30); *Anal.* for $C_7H_{15}ClS$:

calc : C, 50.43 ; H, 9.06 ; S, 19.23 ; Cl, 21.27,

found : C, 50.50 ; H, 8.84 ; S, 19.17 ; Cl, 21.46.

The dipentyl thioacetal which was carefully collected at 105° C (0.6 torr) showed the following spectroscopic data : ^1H NMR : δ = 0.88 (t, 6H, 2 CH_3), 1.25-1.65 (b.m, 12H, 2 {-$(CH_2)_3$ }), 1.55 (d, 3H, **C**H_3-CH($SC_5H_{11})_2$), 2.32 (m, 4H, 2 (-CH_2-S-)), 3.85 (q, 1H, CH_3-C**H**-S); ^{13}C NMR : δ = 13.8 (2C, 2 CH_3), 23.1 (**C**H_3-CH-), 22.2, 29.1, 30.2 (2C each, CH_2's), 31.1 (2C, 2(**C**H_2-S)), 46.0 (1C, -**C**H-($SC_5H_{11})_2$); MS (EI), m/z (%) : 234 (M^+, 25), 131 (M^+ - C_5H_{11}-S, 100), 75 (69), 69 (42), 61 (30), 55 (12).

n.Pentyl vinylsulfide 78.

A four-necked round-bottomed flask was equipped with a mechanical stirrer, a thermometer, a reflux condenser, and a dropping funnel. The flask was charged with 25.0 g (0.167 mol) of freshly distilled diethylaniline, and then heated at 90° C. The distilled chlorothioether **77** (27.6 g, 0.167 mol) was then added drop-wise, after which the temperature was maintained at 90° C for an hour with gentle stirring. As the reaction proceeded a precipitate of diethylaniline hydrochloride formed. After cooling, the semi-solid reaction mixture was shaken with 20 ml of concentrated hydrochloric acid and 35 g of ice. The upper organic layer was then separated, rewashed with 10% hydrochloric acid and water, and

dried with $MgSO_4$. Distillation of the crude mixture afforded 33 % of pure n.pentyl vinylsulfide with a boiling point of 40 - 43° / 0.95 torr; ^1H NMR : δ = 0.90 (t, 3H, CH_3), 1.24-1.44 (b m, 4H), 1.55-1.68 (m, 2H, -C**H**$_2$-CH_2S), 2.69 (t, 2H, CH_2S), 5.12 (dd, 2H, H_2C=), 6.34 (dd, 1H, =CH-S).

1,2-dibromoethyl n.pentyl sulfide 79.

a) Directly *via* **1-chloroethyl n.pentyl sulfide 77.**

In a 2-necked round-bottomed flask fitted with a thermometer and a dropping funnel was placed 83.35 g (0.50 mol) of **77** and a stirrer bar. To the above stirred solution was added 79.91 g , 25.76 ml, of bromine (0.50 mol) slowly so that the internal temperature was kept at 35° C. After the addition of Br_2 was complete the mixture was stirred for another 15 min. The dissolved hydrogen halides were removed by evacuation to give the dibromide; TLC, R_f = 0.70 (1 : 1 / ethyl acetate : hexane). Purification of the crude product was not attempted as the reaction went so smoothly that the dibromide was the only detectable product (TLC, ^1H nmr, ^{13}C nmr, MS). Due to the suspected instability of this compound it was used immediately after its preparation in the subsequent reaction.

The structure of the compound was evident from its spectral data : ^1H NMR : δ = 0.91 (t, 3H, C**H**$_3$-), 1.29 - 1.44 (m, 4H, CH_3-(C**H**$_2$)$_2$-), 1.61 - 1.71 (m, 2H, - C**H**$_2$-CH_2- S), 2.78 (m, 2H, - C**H**$_2$ - S), 3.84 - 4.07 (m, 2H, C**H**$_2$Br - CHBr-), 5.34 (m, 1H, -C**H**Br); ^{13}C NMR : δ = 14.1 (CH_3), 22.1, 28.0, 30.8 (CH_3-(**C**H_2)$_3$-), 32.6 (-CH_2-S), 35.5 (CH_2Br), 58.8 (-CHBr); MS (EI), m/z (%) : 288 (M^+, 4), 209 (M^+ -Br, 48), 153 (22), 130 (14), 80 (35), 69 (100).

b) *Via* **ethenyl n.pentyl sulfide 78.**

A solution of 12.5 g (78.0 mmol) of bromine in 29 ml of carbon tetrachloride was added under an argon atmosphere and at -10° C to a stirred solution of 10.0 g (76.8 mmol) of n.pentyl vinylsulfide **78** in carbon tetrachloride (20 ml). When the addition was complete, the reaction mixture was further stirred at -10° C for 15 min, then allowed to warm up to room temperature. The dibromosulfide was either isolated by washing the pale yellow solution with 5% thiosulfite, drying and evaporation of carbon tetrachloride in vacuo (20 torr), or used directly as a carbon tetrachloride solution for the preparation of 2-bromoethenyl-1-n.pentyl sulfide **80**.

2-Bromoethenyl-1-n.pentyl sulfide 80.

The above carbon tetrachloride solution of1,2-dibromoethyl n.pentyl sulfide was added drop-wise, while stirring, to 13.5 g, (90.0 mmol) of freshly distilled diethylaniline which was heated at 80° C. After the addition was complete, stirring at the same temperature was continued for 0.5 hr. After cooling, water was added and the organic layer was separated, washed with cold 2N hydrochloric acid and water, and dried with Na_2SO_4. Evaporation of carbon tetrachloride resulted in a dark brown oil which was distilled to afford 43% of 2-bromoethenyl-1-n.pentyl sulfide **80**; b.p. 40-46° C / 0.1 torr. ^1H NMR analysis showed that the product was predominantly (90%) the cis-isomer.

The title compound showed the following spectral data : ^1H NMR : δ = 0.84 (t, 3H, CH_3), 1.26-1.32 (m, 4H, CH_2's), 1.59 (m, 2H,

CH_2), 2.70 (t, 2H, CH_2-S) 6.12, 6.72 (each d, J = 8 Hz, 2H, CH=CH) ; ^{13}C NMR : δ = 13.8 (CH_3), 22.1, 30.0, 30.5, 33.2 (4 CH_2's), 102.3, and 132.5 (olefinic carbons); MS (EI), m/z (%) : 210 ($M^+ + 2$, 71), 208 (M^+, 70), 138 (100), 129 (M^+ -Br, 10), 71 (32).

Attempted dehydrohalogenation of **cis-2-bromoethenyl-1-n.pentyl sulfide 80** using potassium hydroxide.

3.38 g of **80** (16.0 mmol) was mixed with 2.68 g (40.0 mmol) of potassium hydroxide and the mixture heated at 120° C for two hours. The temperature of the bath was then gradually raised to 150° C, and the mixture was then cooled and water was added. The aqueous layer was extracted with ether (3 x 25 ml). The ether extract was washed with brine and dried over Na_2SO_4. Evaporation of ether gave a brown residue, which was distilled on the kugelrohr. ^1H NMR and IR analysis of the distilled material showed no acetylenic functionality. The distilled material was not identified.

Phase Transfer Catalysis Methods For Dehydrohalogenation of 79.

a) using KOH.

Freshly and finely powdered potassium hydroxide (0.25 mol, 14.0 g) and 100 ml of petroleum ether (b.p. = 45° C, 100 ml) were placed in 3-necked round-bottomed flask equipped with a mechanical stirrer, a dropping funnel and a reflux condenser. To the above suspension was added 0.100 mmol (26.0 mg) of 18-crown-6 and the mixture was stirred and heated to reflux. 1,2-Dibromoethyl n.pentyl sulfide was then added drop-wise and the refluxing continued for 9

hr (see also table 2). At the end of the refluxing period, the mixture was cooled, filtered, and the solvent removed. Vacuum distillation produced only traces of the desired ethynyl sulfide **81**. The major products were 1-bromoethene-1-n.pentyl sulfide **82** and 1,4-bis-(n.pentylthio) acetylene **83**.

1-bromoethene-1-n.pentyl sulfide had a b.p. of 50-52° C / 0.6 torr; TLC, R_f = 0.67 (100% ethyl acetate). The compound exhibited the following spectral data : IR (neat) : υ = 748 (C-Br), 1581 (C=C) cm^{-1}; ^1H NMR : δ = 0.91 (t, 3H, CH_3), 1.33-1.43 (b. m, 4H, $-(CH_2)_2-$), 1.63 (qu, 2H, CH_2), 2.77 (t, 2H, CH_2-S), 5.70, 5.87 (each d, $=CH_2$) ; ^{13}C NMR : δ = 13.8, 22.1, 28.1, 30.9, 34.8, 120.1, 125.3.

An attempt to dehydrobrominate **82** using KOH in a phase transfer catalysis in a similar way as stated above failed and the major product was 1,4-bis-(n.pentylthio) acetylene **83** which showed the following spectral data : IR (neat) : υ = 2928, 2858, 1465 cm^{-1}; ^1H NMR : δ = 0.90 (b t, 6H, $2CH_3$), 1.34 (m, 8H), 1.64 (b. m, 4H), 2.67 (2 t, 4H, $2(-CH_2S-)$); MS (EI), m/z (%) : 230 (M^+, 18), 206 (31), 160 (9), 103 (19), 71 (56), 55 (24), 43 (100), 29 (68).

b) using t-BuOK.

To a stirred solution of **79** (50.0 mmol, 14.4 g) and 26 mg (0.10 mmol) of 18-crown-6 in 50 ml of petroleum ether (b.p. 90 -105° C) was added fresh potassium t-butoxide and the mixture was heated at 90°C for seven hr. The mixture was then cooled and H_2O added. The organic layer was separated, washed with water and dried over Na_2SO_4. Evaporation of ether and kugelrohr distillation of the crude

product afforded **81** in 22% yield. The other isolated product was (Z)-1-t-butoxy-2-n.pentylthioethene **84** (10%). In an attempt to increase the yield of **81** by varying the conditions of reaction (see table 2) **84** appeared to be the predominant product.

(Z)-1-t-Butoxy-2-n.pentylthioethene **84** , b.p 62° C / 0.9 torr, exhibited the following spectral data : IR (neat) υ = 1726, 1613 cm^{-1} ; ^1H NMR : δ = 0.89 (t, 3H, CH_3), 1.25-1.40 (b m, 4H, CH_2's), 1.30 (s, 9H, $(CH_3)_3$-C), 1.66 (m, 2H, -C**H**$_2$-CH_2S), 2.63 (t, 2H, CH_2-S), 4.90, 6.43 (each d, J = 4 Hz, CH=CH); ^{13}C NMR : δ = 14.1 (CH_3), 22.5 (CH_3-**C**H_2-), 28.2 (3C, (**C**$H_3)_3$), 29.9, 31.0, 33.9 (CH_2's), 77.0 (**C**-$(CH_3)_3$), 100.5 , 139.8 (2C, **C**H=**C**H) ; MS (EI), m/z (%) : 202 (M^+, 31), 146 (100), 129 (25), 71 (6), 57 (15).

Acetylenic thioether 81 from 84 :

a) using BuLi in ether.

A solution of 19.8 mmol of n.butyllithium in hexane, that is, 14.1 ml of 1.4 M of n.butyllithium in hexane, was added, in an argon atmosphere, to a cold (-30°) solution of 1-t-butoxy-2-n.pentylthioethene **84** (9.90 mmol, 2.00 g) in dry ether (10 ml). The solution was stirred at - 30° C for 5 minutes then was allowed to warm up to room temperature and further stirred for 15 minutes. The reaction mixture was then hydrolysed by the addition of water and worked up with ether. The ether layer was separated and dried over Na_2SO_4. Evaporation of the ether and distillation of the remaining brown residue afforded the acetylenic thioether **81** in 8 % yield and 25 % of starting material. The identity of **81** was confirmed by its spectral data.

b) using sodium amide in liquid ammonia.

To a well stirred suspension of sodium amide (1.87 g, 48.0 mmol) in liquid ammonia (25 ml) was added (dropwise) 4.85 g (24.0 mmol) of (Z)-1-t-butoxy-2-n.pentylthioethene **84**. The dropping funnel containing the sulfide was rinsed with small amounts of dry ether. The mixture was then stirred mechanically at the boiling point of liquid ammonia for four hours. The next day when all the ammonia was evaporated, the residue was treated with ether and water. After separation, the aqueous layer was shaken with ether, and the combined etheral layers dried over anhydrous $MgSO_4$. After all the ether was removed in vacuo, the remaining brown oil was distilled giving the acetylenic thioether **81** in 21% yield, together with 15% of starting material.

Double dehydrohalogenation of 79 using sodium amide in liquid NH_3 .

Ethynyl n.pentyl sulfide 81.

To a 5-liter 3-necked round-bottomed flask charged with 2 liters of liquid ammonia (passed through glass tubing filled with KOH pellets) 68.27 g (1.75 mol) of sodium amide was added quickly via a long-stem funnel. To the above suspension was added (drop wise) at -40° C with vigorous stirring 144.20 g (0.50 mol) of the dibromide **79**, freshly prepared from the chloro thioether **77**. After the addition was complete, the suspension was further stirred for 1 hr at the boiling point of liquid ammonia. The ammonia was then allowed to evaporate overnight with all necks of the flask closed

except one which was connected to a drying tube filled with KOH pellets. The next day, the mixture was worked up by the addition of H_2O and ether. After separation, the ether layer was isolated and the aqueous layer was extracted with ether (4 x100 ml). The combined ether extracts were dried over anhydrous $MgSO_4$ and the ether was then evaporated. The dark residue was then fractionally distilled at reduced pressure and ethynyl n.pentyl sulfide **81** (70%) was collected at 30° C / 1.0 torr, the receiving flask being cooled at -30° C. Ethynyl n.Pentyl sulfide (TLC, R_f = 0.75 (1 : 1 / ethyl acetate : hexane)) is colourless when first collected by distillation and it changes to pale yellow and then to orange colour upon standing at room temperature. The compound is stable for at least 8 months if kept at -20° C with the exclusion of air.

The structure of the compound was confirmed by its spectral data : IR (neat) 1446, 2043 (C≡C), 3295 (≡CH) cm^{-1}; ^1H NMR : δ = 0.92 (t, 3H, CH_3), 1.33 -1.43 (b m, 4H, CH_3-(CH_2)$_2$ -), 1.76 (qu, 2H, -CH_2- CH_2-S), 2.69 (s, 1 H, HC≡C), 2.75 (t, 2H, -CH_2- S); ^{13}C NMR : δ = 13.8 (CH_3), 22.1 , 28.8, 30.3 (3 CH_2's), 35.1 (CH_2-S), 74.7, 81.8; MS (EI), m/z (%) : 128 (M^+, 72), 113 (M^+ - CH_3, 20), 99 (30), 71 (100); exact mass calculated for $C_7H_{12}S$ (M^+) 128.0660 found 128.0673. *Anal.* for $C_7H_{12}S$:

calc. C, 65.65 ; H, 9.44 ; S, 25.04

found C, 65.69 ; H, 9.50 ; S, 25.10

II-3. **trans-** 2 **- Iodoethenyl n.pentyl sulfide 85.**

To a solution of **81** (0.285 g, 2.22 mmol) in dry THF (10 ml) at room temperature was added solid zirconocene chloride hydride

(0.584 g, 2.27 m mol). The mixture was then stirred as it gradually became clear yellow solution (10 min). TLC monitoring of the reaction indicated the complete consumption of the terminal acetylene in about 20 min.

The reaction mixture was then treated with solid N-iodosuccinimide (0.500 g, 2.22 mmol) and stirred at room temperature for half an hour. Upon completion as monitored by TLC, the reaction mixture was diluted with hexane (10 ml) and transfered to a separatory funnel where it was separated and the organic extract was washed with 5% sodium hydrogen carbonate and saturated sodium chloride. The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue on silica gel, using ethyl acetate as elutant, gave 90% of the vinyl sulfide in over 98% selectivity in favour of the E-isomer.

This vinyl sulfide exhibited the following spectral data : ^1H NMR : δ = 0.90 (t, 3H, CH_3), 1.32-1.39 (m, 4H, CH_3-(CH_2)$_2$-), 1.64 (m, 2H, -CH_2-CH_2-S), 2.70 (t, 2H, -CH_2-S), 5.87 , 6.88 (each d, 2 H, J =14 Hz, olefinic protons); ^{13}C NMR : δ = 13.9 (CH_3), 22.2 , 28.9, 30.8 (CH_2's), 32.5 (CH_2-S), 66.7 (C=CH-S), 136.4 (I-CH=C); MS (EI), m/z (%) : 256 (M^+, 0.5), 254 (M^+ -2H, 100), 206 (23), 128 (M^+- HI, 25), 127 (33), 103 (5), 71 (23).

cis-Iodoethenyl n.pentyl sulfide 86.

When a sample of the trans-vinyl sulfide **85** was kept as a THF solution at -10° C for six months, it isomerized almost completely to the cis-isomer. ^1H NMR analysis of the cis-isomer gave a spectrum similar to that of the trans-isomer. The chemical shifts

for the protons of the alkyl chain were identical except for the CH_2-S protons which gave a triplet at δ 2.82, and the olefinic hydrogens which gave signals at δ 6.23 , 7.04 (each d, J = 6 Hz, 2 olefinic protons).

III- Preparation of the upper (α) side-chain equivalent. Synthesis of methyl 7-bromoheptanoate 90.

(i) 5-Chloropentyl acetate 93.

A mixture of 78.5 g (1.00 mol.) of redistilled acetyl chloride, 94.7 g (1.10 mol) of tetrahydropyran (dried over sodium flakes and distilled) and five grams of freshly fused ground zinc chloride was heated for 1 hr on a steam bath. When cooled the mixture was diluted with 225 ml of benzene and shaken with 150 ml of cold water until the brown colour had changed to yellow and the benzene layer separated off. The benzene layer was then washed with 150 ml of cold saturated sodium hydrogen carbonate, separated and dried over Na_2SO_4.

Evaporation of benzene gave 152 g (92% yield) of pure product which was used as such for further transformations. TLC analysis indicated only one spot with R_f = 0.63 (7 : 3 / ethyl acetate : hexane). The compound showed the following spectral data : IR (neat) : υ = 1739 (ester) cm^{-1}; ^1H NMR : δ = 1.43-1.81 (m, 6H , $(CH_2)_3$-CH_2O) , 2.01 (s, 3H , CH_3C=O), 3.51 (t, 2H, CH_2-Cl), 4.04 (t, 2H, CH_2-O-); ^{13}C NMR : δ = 20.3 (CH_3), 22.9, 27.5, 31.7 (3 CH_2's), 44.2 (CH_2-Cl), 63.6 (CH_2-O-), 170.2 (C=O); MS (EI), m/z (%) : 121 (M^+ - C_2H_3O, 5), 104 (M^+ -CH_3CO_2H, 45), 73 (80).

(ii) 7 - Bromoheptanoic acid 91.

A one-liter three-necked round-bottomed flask was fitted with a mechanical stirrer, reflux condenser and a dropping funnel. In the flask was placed 500 ml of dry ethanol and 25.52 g of metallic sodium was gradually added through the condenser. When all the sodium had dissolved, the ethoxide solution was allowed to cool to room temperature and was treated with 177.8 g (1.11 mol) of redistilled diethyl malonate. The solution was then stirred, heated to gentle boiling, and charged with 6.9 g of NaI.

To the above refluxing mixture, 149.6 g (0.91 mol) of 5-chloroamyl acetate was added drop-wise over a period of 40 min, which resulted in a brown suspension. The suspension was allowed to cool and the solution was decanted. After removal of ethanol and ethyl acetate by distillation, the cooled reaction mixture was added to 10% H_2SO_4, and the product, after saturation of the aqueous layer with ammonium sulphate, isolated with benzene.

The solvent free oil of the lactone ester **92** obtained above was mixed with glacial acetic acid (175 ml) and constant boiling hydrobromic acid (175 ml) and the resulting mixture slowly distilled through a 20-cm Vigreux column, resulting in the collection of about 125 ml of ethyl acetate containing some ethyl bromide. The decarboxylation which by that stage had already started was completed by addition of 20 ml of concentrated H_2SO_4 and further refluxing for 1 h.

The cooled solution was then mixed with another portion of constant boiling hydrobromic acid (175 ml) and 53 ml of concentrated sulphuric acid, and the mixture heated at 110° C for 4

hours. The reaction mixture was then allowed to cool to room temperature, diluted with H_2O and the lower layer of bromo-acid separated. The aqueous layer, previously saturated with ammonium sulphate, was extracted twice with ether. The combined organic extracts were then washed with H_2O, dried over Na_2SO_4, treated with charcoal and evaporated to give 115 g of crude bromo-acid. Fractional distillation afforded 7-bromoheptanoic acid **91** as an almost colourless oil, b.p. 124° C / 0.7 torr (lit.[19] b. p. 140 - 142° C /1.5 torr) which solidified and had a melting point of 28 ° C (lit.[19] m. p. 28-29° C); TLC, R_f = 0.37 (5 : 5 / ethyl acetate : hexane).

The structure of the compound was also confirmed by its spectral data : IR (neat) : υ = 728 (C-Br), 1709 (C=O), 3000 (OH) cm^{-1}; ^1H NMR : δ = 1.31-1.51 (m, 4H, $-(CH_2)_2-$), 1.58-1.73 (qu, 2H, $-CH_2-$), 1.80-1.94 (qu, 2H, $-CH_2-$), 2.37 (t, 2H, $-CH_2-CO$), 3.41 (t, 2H, $Br-CH_2-$), 11.70 (b s, 1H, disappears on D_2O exchange, acidic hydrogen); ^{13}C NMR : δ = 24.3, 27.7, 28.1, 32.4, 33.6, 33.9, 180.2 (C=O); MS (EI), m/z (%) : 149 ($M^+ - C_2H_3O$, 13), 129 (M^+ - Br, 13), 111 (18), 69 (33), 60 (100), 55 (28).

(iii) Methyl 7-bromoheptanoate 90

A mixture of 63.7 g (0.310 mol) of 7-bromoheptanoic acid, 180 ml of dry benzene, 51 ml of methanol and 1 ml of concentrated sulfuric acid was refluxed with a Dean-Stark phase-separator until no further phase-separation took place. When cooled, the solution was washed with water, sodium hydrogen carbonate solution, and again water. Drying over Na_2SO_4 and evaporation of solvent gave pure methyl ester as an almost colourless liquid; TLC, R_f = 0.43 (1 :

1 / ethyl acetate: hexane).

The structure of the compound was confirmed spectroscopically : IR (neat) : δ = 832 (C-Br), 1739 (C=O) cm^{-1}; ^1H NMR : δ = 1.32-1.43 (m, 4H,), 1.64 (qu, 2H, -CH_2-), 1.86 (qu, 2H,-CH_2-) 2.31 (t, 2H, -CH_2-CO), 3.40 (t, 2H, Br-CH_2-), 3.65 (s, 3H, CH_3O); ^{13}C NMR : δ = 24.0, 27.2, 27.6, 32.0, 32.9, 33.1, 50.5, 172.8 (ester C=O); MS (EI), m/z (%) : 191 (M^+ - OCH_3, 13), 143 (M^+ - Br, 31), 111(13), 83 (22), 74 (100), 69 (13), 55 (3).

IV- Synthesis of the 4-substituted cyclopentenone bearing the α-side chain, synthons 37 and 38.

(i) Ethyl 1-(6'-Methoxycarbonylhexyl)-2-oxocyclo pentane carboxylate 19.

A 1-L 3-necked round-bottomed flask was fitted with an efficient mechanical stirrer, a reflux condenser (the upper end of which was connected to a bubbler) and a dropping funnel with a side arm for dry argon inlet. The flask was charged with 13.5 g of 60% (0.337 mol) sodium hydride (washed free of oil with dry hexane) and 320 ml of dry dimethoxyethane.

To the above stirred suspension was added 49.5 g (0.317 mol) of ethyl 2-oxocyclopentane carboxylate during 35 min while maintaining a temperature of 25° C. When gas evolution was complete, 70.7 g (0.317 mol) of methyl 7-bromoheptanoate **90** was added, and the mixture was refluxed under argon for 26 hr, cooled, and filtered. The solids were washed with ether, and the filtrate and ether washings combined and evaporated. The residue was poured into 200 ml of H_2O and acidified using 10% hydrochloric acid.

Working up with ether gave 80.0 g of orange oil which was partially cleaned on kugelrohr and then chromatographed on silica gel using a 1 : 1 mixture of hexane and ethyl acetate as eluting solvent. TLC analysis (7.5 : 2.5 / ethyl acetate : hexane) showed one component with R_f value of 0.45.

The compound was found to have the following spectral data : IR (neat) υ = 1748 (C=O, ester), 1730 (C=O, ketone) cm^{-1}, ^1H NMR : δ = 1.24 (t, 3H, OCH_2CH_3), 2.25 (t, 2H, CH_2CO_2), 3.67 (s, 3H, OCH_3), 4.17 (q, 2H, OCH_2CH_3); ^{13}C NMR : δ = 13.9 (CH_3), 19.4, 24.4, 24.6, 28.6, 29.3, 32.6, 33.5, 33.8, 37.7 (9 CH_2's), 51.2 (OCH_3), 61.1 (-CH_2-O), 64.0 (quaternary C), 170.9, 173.9 (2 C=O, ester), 214.6 (C=O, ketone).

(ii) 2-(6'-Carbomethoxyhexyl) cyclopentanone 18.

A mixture of 65.5 g (0.218 mol) of **19**, 77 ml of concentrated sulfuric acid, 195 ml of glacial acetic acid, and 273 ml of H_2O was refluxed for 20 hr. When cooled, the mixture was treated with 10% sodium hydrogen carbonate (250 ml) and extracted with ether. The ether extract was washed twice (2 x 400 ml) with H_2O and once with 10% sodium hydrogen carbonate (400 ml). The ether extract was dried (Na_2SO_4) and evaporated to yield 2-(6'-carboxyhexyl) cyclopentanone **16** as an oil. An analytical sample had a boiling point of 159 - 163° C / 0.09 torr; TLC, R_f = 0.30 (5 : 5 / ethyl acetate : hexane).

The distilled pure compound showed the following spectral data : IR (neat) : υ = 3102 (OH), 1748, 1710 cm^{-1}; ^1H NMR : δ = 2.30 (t, 2H, -CH_2COOH), 11.49 (br s, 1H, COOH), ^{13}C NMR : δ = 20.5, 24.3, 25.3, 27.0, 28.1, 28.6 (2C), 29.3, 33.7, 33.9, (10 CH_2's), 48.9 (C-8,

CH), 179.3 (C-1, acid C=O), 221.7 (C-9, ketone C=O); MS (EI), m/z (%) : 212 (M^+, 2), 194 ($M^+ - H_2O$, 2), 84 (M^+ -128 (entire side chain), 100), 83 (16), 73 (17), 69 (25), 68 (18), 60 (50), 55 (41).

The crude oil **16** was esterified in a mixture of dry methanol (250 ml) and dry benzene (800 ml) in the presence of 1.0 g of p-toluenesulfonic acid. The mixture was refluxed in a 2-liter round-bottomed flask fitted with a Dean-Stark separator for 7 hr. When cooled, the mixture was concentrated, poured on 200 ml of 5% sodium hydrogen carbonate, and extracted (2 x 200 ml) with ether. The ether extract was dried (Na_2SO_4) and evaporated to give a red brown oil. Distillation on the kugelrohr produced 37 g (75%) of **18** as an almost colourless oil; b. p. 120-125° C / 0.7 torr (lit.[16] b. p. 135-140° C / 0.4 torr). TLC analysis (8 : 2 / ethyl acetate : hexane) showed a single component with R_f of 0.55.

The structure of the compound was also confirmed by its spectral data : IR (neat) : υ = 1739 (C=O), 1160 cm^{-1} ; ^1H NMR : δ = 1.22-1.32 (m, 8H), 1.55-1.98 (m, 6H), 3.67 (s, 3H, OCH_3); ^{13}C NMR : δ = 20.5, 24.7, 27.1, 28.7, 29.0, 29.4 (2 carbons), 33.8, 37.9, 48.8 (C-8), 51.1 (OCH_3), 173.9 (C-1, ester C=O), 221.0 (C-9, ketone C=O); MS (EI), m/z (%) : 226 (M^+ ,5), 195 ($M^+ - OCH_3$, 9), 143 (5), 11 (10), 97 (9), 84 (100), 69 (10), 55 (25).

(iii) 1-Acetoxy-2-(6'-carbomethoxyhexyl) cyclopent-1-ene 96.

A stirred solution of 28.2 g (0.126 mol) of **18**, 270 mg of p-toluenesulfonic acid and 57.0 ml of acetic anhydride was heated while the acetic acid which was formed was fractionally distilled

off. Acetic anhydride was added periodically to maintain the original volume and when no more acetic acid distilled off the mixture was heated up to 140° C, then cooled and poured onto a stirred ice-cold mixture of 400 ml of saturated sodium bicarbonate and 300 ml of hexane. The organic phase was then worked up in the usual way to yield an oil. Distillation of the product gave 28.6 g (84.6%) of **96** as a colourless oil : b.p. 81-85° C / 0.07 torr; TLC, R_f = 0.57 (8 : 2 / ethyla cetate : hexane).

Spectral analysis of the distilled material indicated the following data : IR (neat) : υ = 1742 (C=O), 1698, 1370, 1212 cm^{-1}; ^1H NMR : δ = 1.25-1.40 (m, 6H), 1.61 (m, 2H), 1.93 (m, 4H), 2.14 (s, 3H, OMe), 2.28 (m, 4H), 2.45 (m, 2H), 3.67 (s, 3H, OCH_3); ^{13}C NMR : δ = 19.7, 20.6 (CH_3-CO), 24.8, 26.2, 26.8, 28.8, 28.9, 30.9, 31.0, 33.9, 51.3 (OCH_3), 126.5 (C-8), 143.9 (C-9), 168.7 (CH_3-C=O), 174.1 (C-1, ester C=O); MS (EI), m/z (%) : 268 (M^+, 5), 194 (M^+ - [OCH_3 + $OCOCH_3$], 100), 166 (30), 123 (33), 97 (76), 84 (37), 69 (25), 55 (49).

(iv) 2-(6'-carbomethoxyhexyl) cyclopent-2-en-1-one 12.

A 1/2 L three-necked round-bottomed flask charged with 9.0 g of calcium carbonate and 100 ml of chloroform was fitted with a mechanical stirrer and two dropping funnels. To the above ice-cooled well-stirred mixture were added simultaneously during 15 min. a solution of 22.5 g (83.3 mmol) of 1-acetoxy-2-(6'-carbomethoxyhexyl) cyclopent-1-ene **96** in 10 ml of chloroform and a solution of 13.4 g (83.8 mmol) of bromine in 10 ml of carbon tetrachloride. The mixture was stirred with cooling for 0.5 hr at 5°

C and the organic layer was then separated, washed with 5% sodium thiosulfate, water and saturated brine, dried and evaporated in vacuo at < 40° C to yield bromo-ketone **17**.

The crude bromo-ketone **17** was then immediately added to a refluxing well-stirred mixture of 16.5 g (0.190 mol) of anhydrous lithium bromide and 16.5 g (0.223 mol) of anhydrous lithium carbonate in 200 ml of dry dimethylformamide. The mixture was refluxed for 0.5 hr under argon. The mixture of lithium salts and DMF was made anhydrous before use by azeotropic distillation of water with benzene and then distillation of benzene. The mixture was then cooled, poured into 1 L of water, acidified with 10% hydrochloric acid, and worked up with ether. The ether extract was washed with water and brine, dried over Na_2SO_4 and concentrated to give 16.0 g of oil. Distillation of the crude product gave 13.5 g (71.9 %) of almost pure **12**, b. p. 95° C / 0.05 torr (lit[16]. b. p. 145-150° C / 0.2 torr). This was further purified by column chromatography on silica gel using hexane / ethyl acetate gradient as elutant; TLC, R_f = 0.39 (5 : 5 / ethyl acetate : hexane).

The chromatographed material showed the following spectral data : IR (neat) : υ = 1736 (C=O, ester), 1703 (C=O), 1633 (C=C) cm^{-1}; ^1H NMR : δ = 1.30-1.66 (b. m, 8H), 2.16 (m, 2H, allylic), 2.56 (m, 2H, allylic), 3.66 (s, 3H, OCH_3), 7.33 (m, 1H, vinylic); ^{13}C NMR : δ = 24.6, 24.8, 26.3, 27.5, 28.8, 28.9, 34.0, 34.5, 51.4 (OCH_3), 146.3 (C-8, olefinic carbon), 157.3 (C-12, olefinic carbon), 174.1 (C-1, ester C=O), 209.9 (C-9, ketone C=O); MS (EI), m /z (%) : 224 (M^+, 13), 193 ($M^+ - OCH_3$, 43), 150 (53), 123 (42), 109 (75), 96 (100).

(v) 4-Bromo-2-(6'-carbomethoxyhexyl)-2-cyclopentenone 11.

A stirred mixture of 6.00 g (26.8 mmol) of **12**, 5.52 g (31.0 mmol) of N-bromosuccinimide (recrystallized from water), 19 mg of 2,2-azadiisobutyronitrile (AIBN) in 25 ml of CCl_4 was refluxed and the consumption of the bromo-ketone was monitored by ^1H NMR. After five hours, the reaction mixture was cooled to 5° C and filtered. The cake was washed with cold CCl_4 (3 x 20 ml) and the filtrate, and carbon tetrachloride washes were combined. After washing with cold water and cold 5% sodium thiosulfate, the carbon tetrachloride extract was dried and evaporated to give 8.47 g of brown-orange oil. This crude product was used as such without further purification. The identity of the compound was confirmed with ^1H NMR and MS analysis : ^1H NMR : δ = 5.01 (b. m, 1H, C-11 proton), 7.59 (m, 1H, vinylic proton); MS (EI), m/z (%) : 303 (M^+ +2, 3), 301 (M^+ , 3), 191 (M^+ - {Br + OCH_3},100), 163 (48), 95 (67), 79 (63).

(vi) 2-(6'-Carbomethoxyhexyl)-4-hydroxy-2-cyclopentenone (±)-1.

The crude bromo-ketone (8.47 g) was refluxed in 1 : 1 mixture of dioxane and water 80 ml for 2.5 hours during which the reaction was monitored by TLC. The reaction mixture was then cooled, the solvent evaporated, and the aqueous layer extracted with $CHCl_3$ (4 x 40 ml). The organic extract was then dried ($MgSO_4$) and evaporated to give 6.0 g of red-brown oil which was stored in the fridge overnight. The next day, the crude product was subjected to column

chromatography using silica gel (200 g) and gradient benzene-ethyl acetate as elutant (100% benzene-0% ethyl acetate to 0% benzene-100% ethyl acetate).

Collection of the pure common fractions gave 4.00 g of (±)-**1** (62 %); TLC, R_f = 0.19 (3 : 7 / ethyl acetate : hexane). The pale yellow material crystallized when cooled, m.p. 46-48° C (lit.[11] m.p. 48-49° C). The compound was characterized spectroscopically and found to have the following data: IR (neat) υ = 3415 (OH), 1735 (C=O, ester), 1695 (C=O, ketone), 1630 (C=C) cm^{-1}; ^1H NMR : δ = 1.26-1.64 (b m, 8H), 2.13-2.36 (m, 5H), 2.80 (dd, 1H, J = 14 Hz, 6 Hz), 3.67 (s, 3H, OCH_3), 3.45-3.95 (b. s, 1H, OH), 4.93 (m, 1H, C**H**-OH, C-11 proton), 7.19 (m, 1H, vinylic); ^{13}C NMR : δ = 24.3, 24.7, 27.1, 28.7, 28.8, 34.0, 44.8, 51.4 ($O\mathbf{C}H_3$), 68.4 (C-11), 147.0 (C-12), 155.9 (C-8), 174.0 (C-1, ester C=O), 206.3 (C-9, ketone C=O) ; MS (EI), m/z (%) : 240 (M^+ , 2), 222 ($M^+ - H_2O$, 33), 190 (89), 163 (33), 111 (48), 95 (100), 83 (28), 69 (71), 55 (100).

(±)-4-Tetrahydropyranyloxy-2-(6'-carbomethoxy-hexyl)-cyclopent-2-en-1-one 37.

One drop of concentrated hydrochloric acid was added to a mixture of 3.20 g (13.3 mmol) of the hydroxy ester **1** and 3.28 g (40 mmol) of dihydropyran. The mixture was stirred to effect mixing and was allowed to stand at room temperature for four hours. The solution then was diluted with ether, and the resulting ethereal layer was washed successively with saturated sodium hydrogen carbonate, and saturated sodium chloride solution. Drying over $MgSO_4$ and evaporation of the ethereal solution yielded 4.52 g of **37**

as a yellow oil. This oil was subjected to column chromatography using silica gel. The column was eluted with a gradient system of hexane : ethyl acetate (100 : 0 to 0 :100) and 25 ml fractions were collected. Fractions 9 - 12 were combined and evaporated to give 3.10 g of pure **37** as faintly yellow oil ; TLC, R_f = 0.77 (7.5 : 2.5 / ethyl acetate : hexane).

The following spectral data were recorded for the title compound : IR (Nujol) : υ = 1740, 1720, and 1040 cm-1; ^{1}H NMR : δ = 3.66 (s, 3H, OCH_3), 3.85 (m, 2H, -$COCH_2$), 4.83-4.91 (m, 2H, HC-O-CH), and 7.26 (m, 1H, vinylic); ^{13}C NMR (the numbers in parentheses are chemical shifts of the corresponding diasteroisomer; the two peaks of these carbons are approximately of equal hight) : δ = 19.8, 24.4, 24.7, 25.3, 27.1, 28.7, 28.9, 30.8, 33.9, 42.2 (43.2), 51.3 (OCH_3), 62.7 (**C**H_2O), 72.9 (73.0, C-11), 98.4 (98.6, O-**C**H-O), 148.0 (148.2, C-8), 153.5 (155.3, C-12), 174.1 (C-1, ester C=O), 205.8 (206.1, ketone C=O); MS (EI), m/z (%) : 324 (M^+, 0.2), 293 (M^+ - OCH_3, 1), 223 (M^+ - THPO, 12), 191 (25), 163 (22), 85 (100), 67 (27), 55 (37).

(±)-4-Triethylsiloxy-2-(6'-carbmethoxyhexyl)-2-cyclopentenone (±)-**38**.

To a solution of the hydroxy ketone **1** (1.63 g, 6.78 mmol) in dry pyridine (10 ml) was added 1.48 ml triethylsilyl chloride (1.33 g, 8.81 mmol). The mixture was stirred and allowed to warm up. The temperature rose up to 30° C and then dropped to room temperature. After stirring the mixture at room temperature for 10 minutes it was then heated at 50° C for 1.5 hour. The mixture was then cooled, diluted with water (20 ml) and extracted with CH_2Cl_2 (2 x 25 ml).

The CH_2Cl_2 extract was dried (Na_2SO_4) and evaporated. The remaining oil was purified by column chromatography on silica gel (eluent, 3 : 7 / ethyl acetate : hexane). 1.9 g (79%) of pure **38** was collected; TLC, R_f = 0.58 (3 : 7 / ethyl acetate : hexane).

The compound showed the following spectroscopic data : IR (neat) υ = 1738 (C=O, ester) cm^{-1}; ^1H NMR : δ = 0.66 (q, 6 H, (CH_3-CH_2)$_3$-Si), 0.98 (t, 9H, (CH_3-CH_2)$_3$-Si), 3.67 (s, 3 H, OCH_3), 4.88 (m, 1H, C-11 proton), 7.05 (m, 1H, vinylic proton); ^{13}C NMR : δ = 4.7 (3C, (CH_3 - CH_2)$_3$-Si), 6.7 (3C, (CH_3-CH_2)$_3$-Si), 24.4, 24.8, 27.2, 28,81, 29.0, 34.0, 45.5 (CH_2's), 51.4 (OCH_3), 68.8 (C-11), 147.2 (C-8), 156.6 (C-12), 174.2 (C-1, ester C=O), 206.2 (C-9, ketone C=O); MS (EI), m/z (%) : 354 (M^+, 2), 325 (M^+ - C_2H_5, 89), 293 (25), 264 (6), 222 (14), 163 (37), 131 (28), 55 (100).

V - Synthesis Of Simple Cyclopentenone Derivatives as Model Systems For The Conjugate Addition Reaction.

(i) (±)- 4-hydroxy-2-cyclopentenone 44.

A two-necked round-bottomed flask equipped with a mechanical stirrer and a reflux condenser was charged with a solution of furfuryl alcohol (50.0 g, 0.454 mol) in 0.10 M phosphate buffer (1 liter). The mixture was then stirred for a few minutes and the pH was adjusted to 4.1 using a few drops of phosphoric acid. The reaction mixture was refluxed for 15 hours. After the mixture cooled to room temperature, it was extracted twice with toluene (2 x 100 ml) and the aqueous layer was evaporated to dryness. The residue was taken into CH_2Cl_2, dried and evaporated to give 22 g of an oily product. The crude product was purified on a silica gel

column using hexane: ethyl acetate (3 : 2) as the eluent. Evaporation of the pure fractions yielded 18.0 g (45%) of the known (±)-4-hydroxy-2-cyclopentenone **44**; TLC, R_f = 0.34 (100% ethyl acetate).

The compound exhibited the following spectral data: IR (neat) : υ = 1720 (C=O), 3425 (OH) cm^{-1}; ^1H NMR : δ = 2.21 (dd, 1H, J = 2 Hz, 16 Hz, C-5 proton), 2.72 (dd, 1H, J = 6 Hz, 12 Hz, C-5 proton), 5.02 (m, 1H, C-4 proton), 6.19 (d, 1H, C-2 proton), 7.64 (dd, 1H, C-3 proton); ^{13}C NMR : δ = 43.4 (C-5), 69.2 (C-4), 133.7 (C-2), 164.2 (C-3), 207.2 (C-1, C=O); MS (EI), m/z (%) : 98 (M^+, 88), 97 (M^+ - H, 34), 80 (M^+ - H_2O, 3), 70 (67), 55 (77), 43 (100).

(ii) (±)- **4-Tetrahydropyranyloxy-2-cyclopentenone 52.**

In a dry round-bottomed flask was taken the hydroxy cyclopentenone (5.0 g, 0.057 mol) and to this was added dihydropyran (16.0 g, 0.186 mol) and 3 drops of concentrated hydrochloric acid. The mixture was shaken (it becomes slightly warm) and was allowed to stand at room temperature for 3 hours. Water (100 ml) and ether (100 ml) then added to the reaction mixture and the ether extract was washed sequentially with saturated solutions of sodium bicarbonate and sodium chloride. Drying and evaporation of ether yielded 10 g of almost pure product which was finally purified by flashing it through a silica gel column using a mixture of hexane and ethyl acetate (3 : 2) as an eluent. Evaporation of solvent gave 8.90 g (90%) of pure **52** as a colourless oil; TLC, R_f = 0.36 (2 : 3 / ethyl acetate : hexane).

The compound had the following spectral data : IR (neat) : υ = 1710 (C=O) cm^{-1}; ^1H NMR : δ = 1.53-1.73 (m, 6H, tetrahydropyranyl

protons), 2.23-2.45 (m, 1H, C-5 protons), 2.64 - 2.80 (m, 1H, C-5 protons), 3.51 - 3.59 (m, 1H, CH_2 - O), 3.85 - 3.91 (m, 1H, CH_2 - O -), 4.76-5.01- (m, 2H, C-4 proton and O-C**H**-O), 6.20 (d, 1H, C-2 proton) and 7.62 (m, 1H, C-3 proton); ^{13}C NMR (the numbers in parentheses are chemical shifts of the corresponding diasteroisomer; the two peaks of these carbons are approximately of equal hight) : δ = 19.0, 24.8, 30.3, 41.2 (42.3), 62.1 (62.2, **C**H_2-O), 74.4 (74.5, **C**H-O), 98.0 (98.3, O-**C**H-O), 134.7 (134.9, C-2 of cyclopentenone),160.5 (162.3, C-3), 205.3 (205.7, C-1, C=O).

(iii) (±)-**4-Triethylsilyloxy-2-cyclopentenone 53.**

The hydroxy ketone **44** (1.47 g, 0.015 mol) was taken into a 100 ml 2-necked rounded-bottomed flask and 20 ml of dry pyridine was added. To the above stirred yellow solution was added 3.34 ml of triethylsilyl chloride (3.0 g, 0.020 mol) *via* a glass syringe. The mixture became cloudy and the temperature rose up to 36° C. After 30 minutes the suspension was heated at 55° C for 45 minutes, cooled, diluted with water (40 ml) and extracted with CH_2Cl_2 (60 ml). The extract was dried (Na_2SO_4) and evaporated to give an oil which was purified by column chromatography on silica gel (eluent, ethyl acetate : hexane / 2 : 3) giving 2.92 g (92 %) of pure **53** as a pale yellow oil; TLC, R_f = 0.66 (3 : 7 / ethyl acetate : hexane).

The structure of the compound was evident by its spectral data which included : IR (neat) : υ = 1720, 1590 cm^{-1}; ^1H NMR : δ = 0.65 (q, 6H, (CH_3-C**H**$_2$)$_3$-Si), 0.97 (t, 9H, (C**H**$_3$-CH_2)$_3$-Si), 2.22 (m, 1H, C-5 H), 2.68 (dd, 1H, J = 6 Hz, 16 Hz, C-5 H), 4.99 (m, 1H, C-4 H , C**H**-O-), 6.15 (dd, 1H, J = 1.1 Hz, 5.7 Hz, C-2 H), 7.46 (dd, 1H, J = 2.2 Hz, 5.6

Hz, C-3 H); ^{13}C NMR : δ = 4.3 (3C, $(CH_3\text{-}\mathbf{C}H_2)_3Si$)), 6.2 (3C, ($\mathbf{C}H_3$-$CH_2$)Si)), 44.6 (C-5), 70.2 (C-4), 134.0 (C-2), 163.3 (C-3), 205.6 (C-1, C=O); MS (EI), m/z (%) : 212 (M^+, 3), 183 ($M^+ - C_2H_5$, 100), 155 (35), 127 (43), 125 (73), 81 (30), 75 (27).

VI- Conjugate addition reactions.

General : All reactions (addition and transfer) in this section were conducted under an argon atmosphere. Prior to such reactions, the apparatus was evacuated and dried by heating with a heat gun (in some cases under high vacum) and then, after cooling, the system was flushed with dry argon. The typical procedure is illustrated in the synthesis of the protected 15-thia-PGE_1 analog, compound **97**.

Protected **15-Thia-PGE_1 97.**

A 50 ml two-necked round-bottomed flask equipped with a low-temperature thermometer, a stir bar and a septum was charged (after it was dried) with a solution of ethynyl n.pentyl sulfide (61.0 mg, 0.48 mmol) in 3 ml of dry THF. To the above colourless solution was added solid zirconocene chloride hydride (130.0 mg, 0.500 mmol) and the mixture stirred at room temperature under slight argon atmosphere for 30 minutes to yield a yellow solution. This solution was cooled to -70° C and treated via a glass syringe with 0.75 mL of methyllithium (1.4 M in ether, 1.10 mmol) to generate an orange yellow solution. This solution was allowed to warm up to -50° C, stirred for 5 minutes and then recooled to - 70° C.

Concurrently, copper cyanide (43.0 mg, 0.48 mmol) was placed in a 25 ml two-necked round-bottomed flask equipped with a stir

bar and a low-temperature thermometer. The flask was sealed, evacuated and purged with argon as above, and tetrahydrofuran (2 ml) was added via syringe. The resulting slurry was cooled to -70 °C and treated with methylithium in ether (0.38 ml, 0.55 mmol). The mixture was allowed to warm up to -50° C until clear, cooled back to -70° C and then cannulated into the zirconium solution keeping both solutions at -70° C. The flask containing the cyanocuprate solution was washed with 1 ml of THF and the washing was cannulated as above. The mixture was allowed to warm to -50° C for 30 minutes and recooled to -70° C. To the above stirred orange solution was added quickly 4-tetrahydropyranyloxy-2-(6-carbo-methoxyhexyl)-cyclopent-2-en-1-one **37** (80.0 mg, 0.25 mmol) in 2 mL of dry THF. The reaction mixture was allowed to warm to -50° C and stirred at this temperature for 5 hours.

The reaction mixture was then recooled to -70° C and quenched with 20 mL of saturated aqueous ammonium chloride / ammonium hydroxide (9 : 1). The mixture was stirred for 10 minutes and then poured on 40 ml of ether. Vigorous stirring produced a deep blue aqueous layer and a pale yellow organic layer in 30 minutes. The layers were separated and the aqueous layer was extracted three times with 25-mL portions of ether. The combined ether extract was washed twice with 100-mL portions of saturated aqueous ammonium chloride / ammonium hydroxide (9 : 1), dried over sodium sulfate and then filtered through a pad of celite. Evaporation of ether gave 143 mg of a yellow-orange oil. The residue was submitted to flash chromatography on silica gel using a gradient solvent (95 : 5 to 65 : 35 / hexane : ethyl acetate) and collecting 20-ml fractions.

Fractions 15-19 were combined to yield the protected 15-thia PGE_1 (80 mg) in a 60% yield as pale yellow oil.

(±)-trans-2-(6'-Carbomethyoxyhexyl)-3-(E-3"-thia -1"-octenyl)-4-hydroxycyclopentanone 71 (15-thia-PGE_1).

Deprotection was carried out by stirring the protected 15-thia PGE_1 analog (75 mg) in 7 mL of 4 : 2 : 1 acetic acid : water : THF at room temperature for 24 hours. The yellow mixture was then neutralized with solid sodium bicarbonate and worked up with ether. The ether layer was washed once with 10% sodium bicarbonate, dried, and the solvent removed in vacuo to give 39 mg of crude 15 thia-PGE_1.

This material was subjected to column chromatography using five grams of silica gel. Elution with a benzene-ethyl acetate gradient (9 : 1 to 6 : 4 / benzene : ethylacetate) gave 22 mg of pure 15-thia-PGE_1, **71** ; TLC, R_f = 0.30 (3.5% methanol in chloroform). The compound was cleaned even further by preparative high performance liquid chromatography. 50 μL of sample in $CHCl_3$ (27 mM) was injected each time and the compound was collected as it was being recorded on the printer.

The structure of the 15 thia-PGE_1 analog **71** was evident by its spectral data : IR ($CHCl_3$) : υ = 3392, 1746 cm^{-1}; ^1H NMR (200 and 500 M Hz) : δ = 0.92 (t, 3 H, C**H**$_3$), 1.30-1.40 (b. m, 8H), 1.57-1.66 (b. m, 7H), 1.88 (b. s, 1H), 2.0 (m, 1H), 2.16 2.49 (m, 2H), 2.30 (t, 2H), 2.71 (t, 2H), 2.78 (dd, 2 H), 3.67 (s, 3H, OC**H**$_3$), 4.05 (q, J = 8 Hz, 1H, C-11 proton), 5.45 (dd, J = 8 Hz,16 Hz, C-13 olefinic hydrogen), 6.18 (d, J = 16 Hz, C-14 olefinic hydrogen); ^{13}C NMR : δ = 13.9 (**C**H_3), 22.2, 24.8,

26.6, 27.6, 28.9, 29.0, 29.3, 30.9, 32.6, 34.0, 46.0 (11 CH_2's), 51.4 (OCH_3), 54.6 (C-8), 55.5 (C-12), 72.2 (C-11), 127.2 (C-13), 128.1 (C-14), 174.1 (C-1), 214.3 (C-9); MS (CI), m/z (%) : 371 (M^+ + H, 1.5), 252 (M^+ - H_2O, 0.4).

(±)- **3-(E-3'-thia-1'-octenyl)-cyclopentanone 87**.

IR ($CHCl_3$) : υ = 1740 (C=O) cm^{-1}; ^1H NMR : δ = 0.92 (t, 3H, CH_3), 1.25-1.39 (b. m, 8 H), 2.27 (t, 2H), 6.24 (d, J = 16 Hz, 1H), 6.46 (dd, J = 6 Hz, J = 16 Hz, 1H); ^{13}C NMR : δ = 13.8 (CH_3), 21.7, 22.3, 29.1, 30.9, 37.8, 39.2, 43.8, 54.0, 132.6, 141.0, 216.4; MS (EI), m/z (%) : 212 (M+, 66), 141 (M^+ - C_5H_{11}, 64), 109 (M^+ - $C_5H_{11}S$, 57), 91 (32), 85 (100), 67 (21), 55 (43)

(±)-**trans-3-(E-3'-Thia-1'-octenyl)-4-triethylsiloxy-cyclopentanone 89**.

The compound was isolated as a pale yellow oil; TLC, R_f = .54 (3 : 7 / ethyl acetate : hexane). The spectral data of the title compound included the following : IR ($CHCl_3$) : υ = 1742 cm^{-1}; ^1H NMR : δ = 0.56 (q, 6H, $(CH_3C\mathbf{H}_2)_3Si$), 0.92 (t, 12H, $(C\mathbf{H}_3CH_2)_3Si$ and $C\mathbf{H}_3$), 4.02 (q, 1H, C-4 **H**), 5.51 (dd, 1H, J = 7.5 Hz, 15 Hz, C-1' **H**), 6.11 (d, 1H, J = 15 Hz, C-2' **H**); ^{13}C NMR : δ = 4.7 (3C, $(CH_3\text{-}\mathbf{C}H_2)_3Si$), 6.7 (3C, $(\mathbf{C}H_3\text{-}CH_2)_3Si$), 13.9 ($\mathbf{C}H_3$), 22.6, 28.7, 28.9, 29.8, 41.7, 42.6 (6 CH_2's), 53.5 (C-1'), 74.0 (C-4), 127.3, 131.4 (2 olefinic carbons), 214.5 (C=O); MS (EI), m/z (%) : 342 (M^+, 8), 313 (M^+ -29, 26), 271 (14).

(±)-trans-5-(6'-Carbomethoxyhexyl)-4-methyl-2-cyclopenten-1-one 99.

The conjugate addition reaction was basically conducted in the same way as that illustrated above for the 15-thia-PGE1 derivative **97** with the following important changes.

To the flask containing CuCN in ether was added 2 molar equivalents of methyllithium at -70° C. The mixture was then allowed to warm up to -10° C until clear and re-cooled to -70° C before cannulating it the flask containing the zirconium complex. The enone was then added as an ether solution and the mixture was stirred for 4 hours at -50° C and worked up in the usual way. Flash column chromatography on the crude (ethyl acetate : hexane gradient) gave a mixture of **97** and **98**. NMR analysis indicated that the mixture was approximatly 20% of **97** and 80% of **98**.

Rechromatographing the mixture on silica gel, compound **98** was deprotected and dehydrated to yield the enone **99** in 55% overall yield based on enone **37**, as a pale yellow oil; TLC, Rf = 0.49 (6 : 4 / ethyl acetate : hexane).

The title compound showed the following spectroscopic data : IR ($CHCl_3$) : υ = 1707 (C=O, ketone), 1740 (C=O, ester) cm^{-1}; ^1H NMR : δ = 1.11 (d, 3H, J = 4 Hz, C**H**$_3$ on C-4), 2.22 (t, 2H, C-6' C**H**$_2$), 2.58 (dd, 1H, J = 7 Hz, 2 Hz), 3.58 (s, 3H, OC**H**$_3$), 6.00 (dd, 1H, J = 5.7 Hz, 1.8 Hz, C-2 **H**), 7.45 (dd, 1H, J = 5.7 Hz, 2.4 Hz, C-3 **H**); ^{13}C NMR : δ = 17.2 (CH_3), 24.8, 27.1, 28.9, 29.3, 30.5, 34.0 (6 CH_2's), 42.8 (C-5), 51.3 (O**C**H_3), 53.5 (C-4), 132.5 (C-2), 168.2 (C-3), 174.1 (C-7', **C**=O ester), 212.1 (C-1, **C**=O ketone); MS (EI), m/z (%) : 238 (M^+, 4), 207 (M^+ -31, 11), 109 (17), 96 (M^+ -142, 100), 81 (12), 67 (13), 55 (20).

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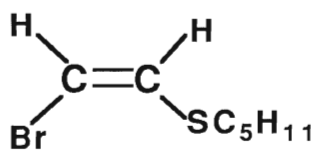
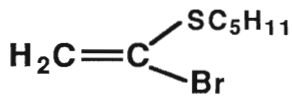
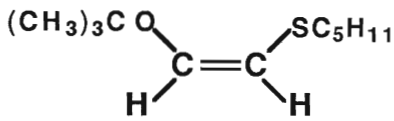
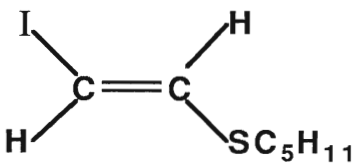
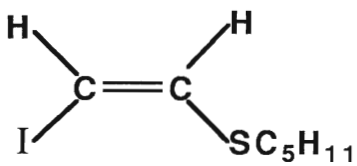
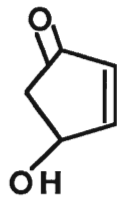
APPENDIX :

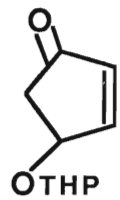
Name of compound	page	structural formula
cis-2-chloroethenyl n.pentyl sulfide **74**.	46	$ClCH = CH - SC_5H_{11}$
cis-bis-(1,2-n.pentylthio) ethylene **73**.	46	$C_5H_{11}SCH = CHSC_5H_{11}$
1-Chloroethyl n.pentyl sulfide **77**.	50	$CH_3-\underset{\displaystyle Cl}{\underset{\vert}{CH}}-SC_5H_{11}$
n.Pentyl vinyl sulfide **78**.	50	$H_2C=CH-SC_5H_{11}$
1,2-dibromoethyl n.pentyl sulfide **79**.	50	$\underset{\displaystyle Br}{\underset{\vert}{CH_2}}-\underset{\displaystyle Br}{\underset{\vert}{CH}}-SC_5H_{11}$
cis-2-bromoethenyl n.pentyl sulfide **80**.	50	

1-Bromoethene-1-n.pentyl sulfide **82**.	53	
1,4-Bis-(n.pentylthio)-acetylene **83**.	53	
(Z)-1-t-Butoxy-2-n.pentyl-thioethene **84**.	53	
Ethynyl n.pentyl sulfide **81**.	53,57	
<u>trans</u>-2-Iodoethenyl n.pentyl sulfide **85**.	59	
<u>cis</u>-2-Iodoethenyl n.pentyl sulfide **86**.	59	

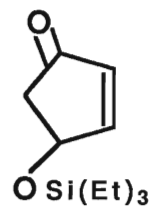
(±)-4-Hydroxy-2-cyclopentenone (±)-**44**. 61



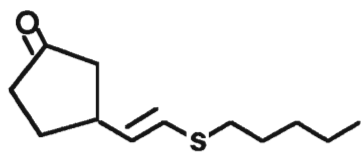
(±)-4-Tetrahydropyranyloxy-2-cyclopentenone (±)-**52**. 61



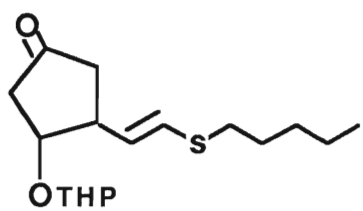
(±)-4-Triethylsiloxy-2-cyclopentenone (±)-**53**. 61



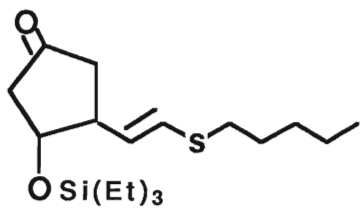
(±)-3-(E-3'-thia-1'-octenyl)-cyclopentanone (±)-**87**. 62

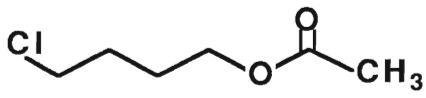
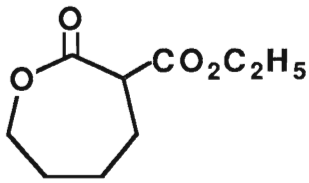
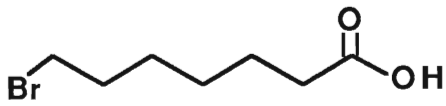
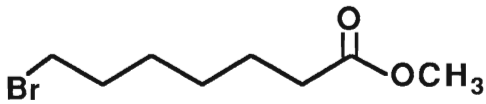
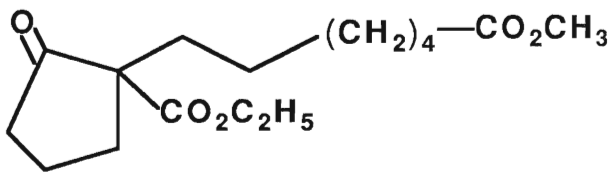


(±)-trans-4-Tetrahydropyranyloxy-3-(E-3'-thia-1'-octenyl)-cyclopentanone (±)-**88**. 62



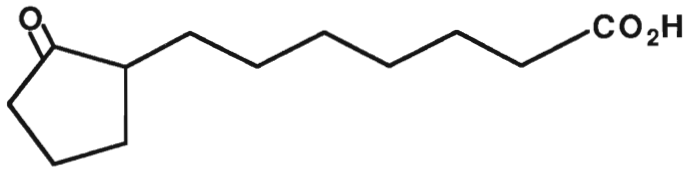
(±)-trans-4-triethylsiloxy-3-(E-3'-thia-1'-octenyl)-cyclopentanone (±)-**89**. 62



5-Chloroamyl acetate **93**.	64	
Ethyl heptanolactone-2-carboxylate **92**.	64	
7-Bromoheptanoic acid **91**.	64	
Methyl 7-bromoheptanoate **90**.	64	
Ethyl 1-(6'-methoxycarbonyl-hexyl)-2-oxocyclopentane carboxylate **19**.	67	

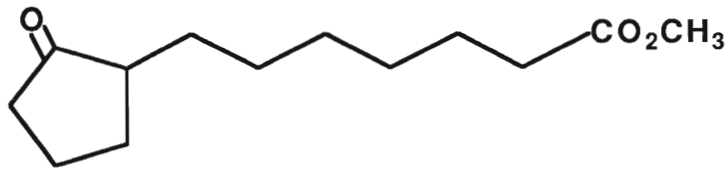
2-(6'-Carboxyhexyl) cyclopentanone **16**.

67



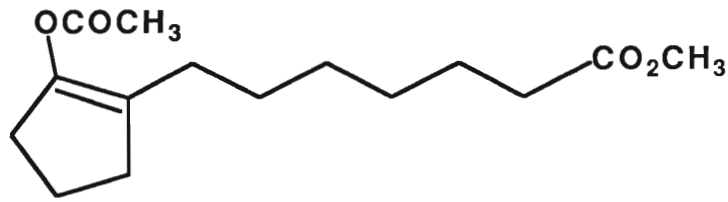
2-(6'-Carbomethoxyhexyl) cyclopentanone **18**.

67



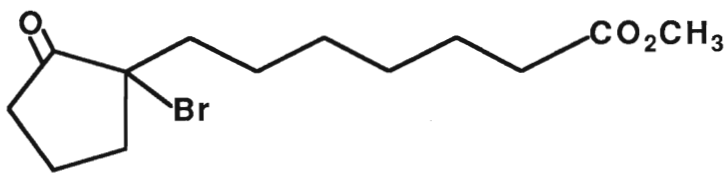
1-Acetoxy-2-(6'-carbomethoxyhexyl) cyclopent-1-ene **96**.

67



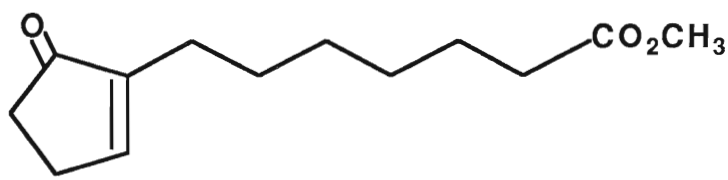
2-Bromo-2-(6'-carbomethoxyhexyl) cyclopentanone **17**.

67



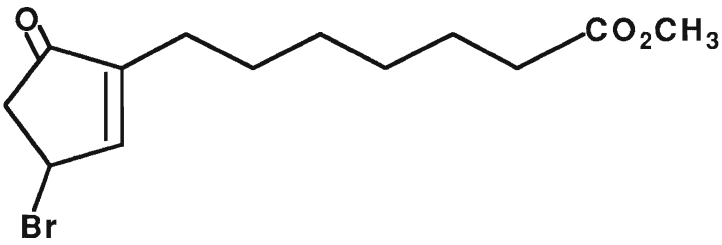
2-(6'-Carbomethoxyhexyl) cyclopent-2-en-1-one **12**.

68



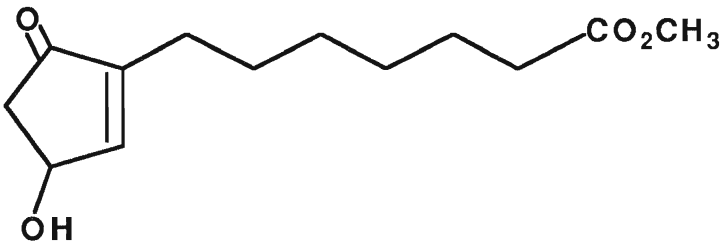
4-bromo-2-(6'-carbomethoxyhexyl)-2-cyclopentenone **11**.

68



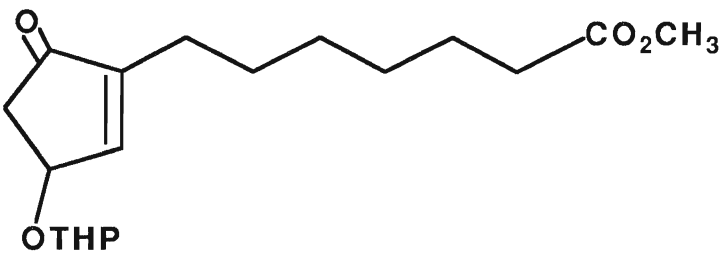
2-(6'-carbomethoxyhexyl)-4-hydroxy-2-cyclopentenone (±)-**1**.

68



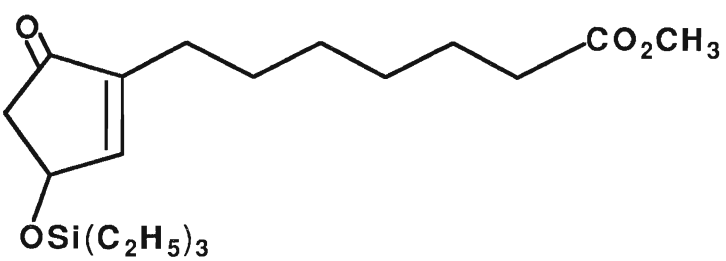
(±)-4-Tetrahydro-pyranyloxy-2-(6'-carbomethoxyhexyl)-2-cyclopentenone (±)-**37**.

68



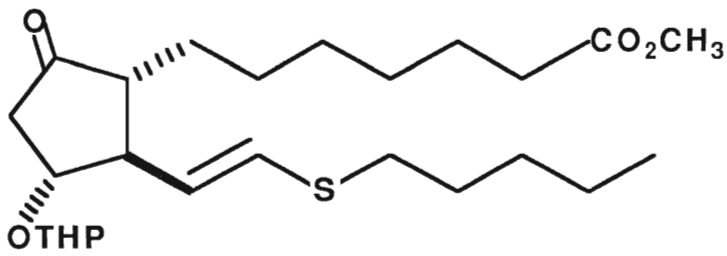
(±)-4-Triethylsiloxy-2-(6'-carbomethoxyhexyl)-2-cyclopentenone (±)-**38**.

68



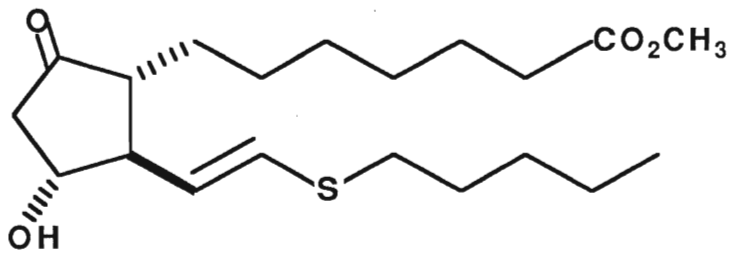
(±)-Tetrahydropyranyloxy-trans-2-(6'-carbomethoxy-hexyl)-3-(E-3"-thia-1"-octenyl) cyclopentanone **97**. ((±)-**11-THP-15-thia-PGE$_1$ methyl ester 97**.)

72



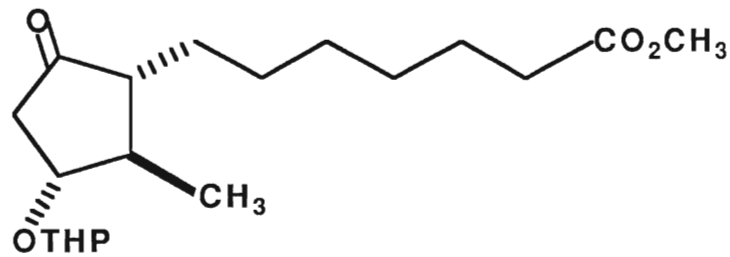
(±)-trans-2-(6'-carbo-methoxyhexyl)-3-(E-3"-thia-1"-octenyl)-4-hydr-oxycyclopentanone **71**. (**15-thia-PGE$_1$ methyl ester** (±)-**71**.)

72



(±)-trans-4-Tetrahydro-pyranyloxy-2-(6'-carbo-methoxyhexyl)-3-methyl cyclopentanone **98**.

77



(±)-trans-4-Methyl-5-(6'-carbomethoxyhexyl)-2-cyclopenten-1-one **99**.

77